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Two European trials of NOLVADEX in women with a high risk of breast cancer were also conducted. They showed no difference in the number of breast cancer cases between the women who took tamoxifen and those who got placebo. These studies had trial designs that differed from that of NSABP P-1, were smaller than P-1, and enrolled women at a lower risk for breast cancer than those in the P-1 trial.

- In women with DCIS, following breast surgery and radiation, NOLVADEX is indicated to reduce the risk of invasive breast cancer. The decision regarding therapy with NOLVADEX for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of NOLVADEX therapy.

  A trial evaluated the addition of NOLVADEX to lumpectomy and radiation therapy in women with DCIS. The primary objective was to determine whether 5 years of NOLVADEX therapy would reduce the incidence of invasive breast cancer in the ipsilateral (the same) or contralateral (the opposite) breast. The incidence of invasive breast cancer was reduced by 43% among women treated wtih NOLVADEX.
- NOLVADEX is used to reduce the recurrence of breast cancer in women who have had surgery and/or radiation therapy to treat early breast cancer. NOLVADEX is also used in women with breast cancer who are at risk of developing a second breast cancer in the opposite breast.

  The Early Breast Cancer Trialists Collaborative Group reviewed the 10-year results of studies of NOLVADEX for early breast cancer. Treatment with NOLVADEX for about 5 years reduced the risk of recurrence of breast cancer and improved overall survival. Treatment with about 5 years of NOLVADEX also reduced the chance of getting a second breast cancer in the opposite breast by approximately 50%, a result similar to that seen in the NSABP P-1 study.
- NOLVADEX is used to treat advanced breast cancer in women and men.

  Three studies compared NOLVADEX to surgery or radiation to the ovaries in premenopausal women with advanced breast cancer and found that NOLVADEX was similar to surgery or radiation in causing tumor shrinkage.

  Published studies have demonstrated that NOLVADEX is effective for the treatment of advanced breast cancer in men.
- NOLVADEX is a prescription tablet available in two dosage strengths: 10 mg tablets and 20 mg tablets. The active ingredient in each tablet is tamoxifen citrate.

How does NOLVADEX work?

NOLVADEX belongs to a group of medicines called antiestrogens. Antiestrogens work by blocking the effects of the hormone estrogen in the body. Estrogen may cause the growth of some types of breast tumors. NOLVADEX may block the growth of tumors that respond to estrogen.

Who should not take NOLVADEX?

- You should not take NOLVADEX to reduce the risk of getting breast cancer if you have ever had blood clots or if you develop blood clots that require medical treatment. However, if you are taking NOLVADEX for treatment of early or advanced breast cancer, the benefits of NOLVADEX may outweigh the risks associated with developing new blood clots. Your health care professional can assist you in deciding whether NOLVADEX is right for you.
- You should not take NOLVADEX to reduce the risk of getting breast cancer if you are taking medicines to thin your blood (anticoagulants) like warfarin (Coumadin®*).
- You should not take NOLVADEX if you plan to become pregnant while taking NOLVADEX or during the two months after you stop taking it because NOLVADEX may harm your unborn child. You should see your doctor immediately and stop taking NOLVADEX if you become pregnant while taking the drug. Please talk with your doctor about birth control recommendations. If you are capable of becoming pregnant, you should start NOLVADEX during a menstrual period or if you have irregular periods have a negative pregnancy test before beginning to take NOLVADEX. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity.
- You should not take NOLVADEX if you are breast feeding.
- You should not take NOLVADEX if you have ever had an allergic reaction to NOLVADEX or tamoxifen citrate (the chemical name) or any of its ingredients.
- NOLVADEX is not known to reduce the risk of breast cancer in women with changes in breast cancer genes (BRCA1 or BRCA2).
- You should not take NOLVADEX to decrease the chance of getting breast cancer if you are less than age 35 because NOLVADEX has not been tested in younger women..
- You should not take NOLVADEX to reduce the risk of breast cancer unless you are at high risk of getting breast cancer. Certain conditions put women at high risk and it is possible to calculate this risk for any woman. Breast cancer risk assessment tools to help calculate your risk of breast cancer have been developed and are available to your health care professional. You should discuss your risks with your health care professional.
- Children should not take NOLVADEX because treatment for them has not been sufficiently studied.

How should I take NOLVADEX?

- Follow your doctor's instructions about when and how to take NOLVADEX. Read the label on the container. If you are unsure or have questions, ask your doctor or pharmacist.
- You will take NOLVADEX differently, depending on your diagnosis.
- For reduction of the risk of breast cancer, the usual dose is 20 mg a day, for five years.
- For treatment of breast cancer in adult women and men; the usual dose is 20–40 mg a day. Take the tablets once or twice a day depending on the tablet strength prescribed. If your doctor has prescribed a different dose, do not change it unless he or she tells you to do so. For women with early breast cancer, NOLVADEX should be taken for 5 years. For women with advanced cancer, NOLVADEX should be taken until your doctor feels it is no longer indicated.
- Take your medicine each day. You may find it easier to remember to take your medicine if you take it at the same time each day. If you forget to take a dose, take it as soon as you remember and then take the next dose as usual.
- Swallow the tablets whole with a drink of water.
- You can take NOLVADEX with or without food.
- Do not stop taking your tablets unless your doctor tells you to do so.

Are there other important factors to consider before taking NOLVADEX?

- Tell your doctor if you have ever had blood clots that required medical treatment.
- Because NOLVADEX may affect how other medicines work, always tell your doctor if you are taking any other prescription or non-prescription (over-the-counter) medications, particularly if you are taking warfarin to thin your blood.
- You should not become pregnant when taking NOLVADEX or during the two months after you stop taking it as NOLVADEX may harm your unborn child. Please contact your doctor for birth control recommendations. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity. You should see your doctor immediately if you think you may have become pregnant after starting to take NOLVADEX.

What should I avoid or do while taking NOLVADEX?

- You should contact your doctor immediately if you notice any of the following symptoms. Some of these symptoms may suggest that you are experiencing a rare but serious side effect associated with NOLVADEX (see **"What are the possible side effects of NOLVADEX?"**)..

  — new breast lumps
  — vaginal bleeding
  — changes in your menstrual cycle
  — changes in vaginal discharge
  — pelvic pain or pressure
  — swelling or tenderness in your calf
  — unexplained breathlessness (shortness of breath)
  — sudden chest pain
  — coughing up blood
  — changes in your vision

  If you see a health care professional who is new to you (an emergency room doctor, another doctor in the practice), tell him or her that you take NOLVADEX or have previously taken NOLVADEX.
- Because NOLVADEX may affect how other medicines work, always tell your doctor if you are taking any other prescription or non-prescription (over-the-counter) medicines. Be sure to tell your doctor if you are taking warfarin (Coumadin) to thin your blood.
- You should not become pregnant when taking NOLVADEX or during the 2 months after you stop taking it because NOLVADEX may harm your unborn child. You should see your doctor immediately if you think you may have become pregnant after starting to take NOLVADEX. Please talk with your doctor about birth control recommendations. If you are taking NOLVADEX to reduce your risk of getting breast cancer, and you are sexually active, NOLVADEX should be started during your menstrual period. If you have irregular periods, you should have a negative pregnancy test before you start NOLVADEX. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity.
- If you are taking NOLVADEX to reduce your risk of getting breast cancer, you should know that NOLVADEX does not prevent all breast cancers. While you are taking NOLVADEX and after you stop taking NOLVADEX and in keeping with your doctor's recommendation, you should have annual gynecological check-ups which should include breast exams and mammograms. If breast cancer occurs, there is no guarantee that it will be detected at an early stage. That is why it is important to continue with regular check-ups.

What are the possible side effects of NOLVADEX?

Like many medicines, NOLVADEX causes side effects in most patients. The majority of the side effects seen with NOLVADEX have been mild and do not usually cause breast cancer patients to stop taking the medication. In women with breast cancer, withdrawal from NOLVADEX therapy is about 5%. Approximately 15% of women who took NOLVADEX to reduce the chance of getting breast cancer stopped treatment because of side effects.

The most common side effects reported with NOLVADEX are: hot flashes; vaginal discharge or bleeding; and menstrual irregularities (these side effects may be mild or may be a sign of a more serious side effect). Women may experience hair loss, skin rashes (itching or peeling skin) or headaches; or inflammation of the lungs, which may have the same symptoms as pneumonia, such as breathlessness and cough; however, hair loss is uncommon and is usually mild

A rare but serious side effect of NOLVADEX is a blood clot in the veins. Blood clots stop the flow of blood and can cause serious medical problems, disability, or death. Women who take NOLVADEX are at increased risk for developing blood clots in the lungs and legs. Some women may develop more than one blood clot, even if NOLVADEX is stopped. Women may also have complications from treating the clot, such as bleeding from thinning the blood too much. Symptoms of a blood clot in the lungs may include sudden chest pain, shortness of breath or coughing up blood. Symptoms of a blood clot in the legs are pain or swelling in the calves. A blood clot in the legs may move to the lungs. If you experience any of these symptoms of a blood clot, contact your doctor immediately.

NOLVADEX increases the chance of having a stroke, which can cause serious medical problems, disability, or death. If you experience any symptoms of stroke, such as weakness, difficulty walking or talking, or numbness, contact your doctor immediately.

NOLVADEX increases the chance of changes occurring in the lining (endometrium) or body of your uterus which can be serious and could include cancer. If you have not had a hysterectomy (removal of the uterus), it is important for you to contact your doctor immediately if you experience any unusual vaginal discharge, vaginal bleeding, or menstrual irregularities; or pain or pressure in the pelvis (lower stomach). These may be caused by changes to the lining (endometrium) or body of your uterus. It is important to bring them to your doctor's attention without delay as they can occasionally indicate the start of something more serious and even life-threatening.

NOLVADEX may cause cataracts or changes to parts of the eye known as the cornea or retina. NOLVADEX can increase the chance of needing cataract surgery, and can cause blood clots in the veins of the eye. NOLVADEX can result in difficulty in distinguishing different colors. If you experience any changes in your vision, tell your doctor immediately.

Rare side effects, which may be serious, include certain liver problems such as jaundice (which may be seen as yellowing of the whites of the eyes) or hypertriglyceridemia (increased levels of fats in the blood) sometimes with pancreatitis (pain or tenderness in the upper abdomen). Stop taking NOLVADEX and contact your doctor immediately if you develop angioedema (swelling of the face, lips, tongue and/or throat) even if you have been taking NOLVADEX for a long time.

If you are a woman receiving NOLVADEX for treatment of advanced breast cancer, and you experience excessive nausea, vomiting or thirst, tell your doctor immediately. This may mean that there are changes in the amount of calcium in your blood (hypercalcemia). Your doctor will evaluate this.

In patients with breast cancer, a temporary increase in the size of the tumor may occur and sometimes results in muscle aches/bone pain and skin redness. This condition may occur shortly after starting NOLVADEX and may be associated with a good response to treatment.

Many of these side effects happen only rarely. However, you should contact your doctor if you think you have any of these or any other problems with your NOLVADEX. Some side effects of NOLVADEX may become apparent soon after starting the drug, but others may first appear at any time during therapy.

This summary does not include all possible side effects with NOLVADEX. It is important to talk to your health care professional about possible side effects. If you want to read more, ask your doctor or pharmacist to give you the professional labeling.

How should I store NOLVADEX?

NOLVADEX Tablets should be stored at room temperature (68–77°F). Keep in a well-closed, light-resistant container. Keep out of the reach of children.

Do not take your tablets after the expiration date on the container. Be sure that any discarded tablets are out of the reach of children.

This leaflet provides you with a summary of information about NOLVADEX. Medicines are sometimes prescribed for uses other than those listed. NOLVADEX has been prescribed specifically for you by your doctor. Do not give your medicine to anyone else, even if they have a similar condition because it may harm them.

If you have any questions or concerns, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about NOLVADEX written for health care professionals that you can ask to read. For more information about NOLVADEX or breast cancer, call 1-800-34 LIFE 4.

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Shown in Product Identification Guide, page 306

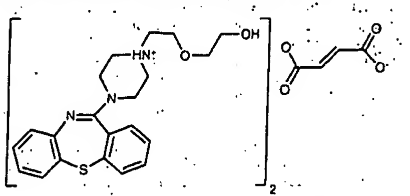
SEROQUEL® ℞

[serō-quĕl]
(quetiapine fumarate)
Tablets

DESCRIPTION

SEROQUEL (quetiapine fumarate) is an antipsychotic drug belonging to a new chemical class, the dibenzothiazepine

derivatives. The chemical designation is 2-[2-(4-dibenzo [b,f] [1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (peach), 100 mg (yellow), 200 mg (round, white), and 300 mg (capsule-shaped, white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50}s=717 & 148nM, respectively), dopamine D_1 and D_2 (IC_{50}s=1268 & 329nM, respectively), histamine H_1 (IC_{50}=30nM), and adrenergic α_1 and α_2 receptors (IC_{50}s=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50}s>5000 nM).

The mechanism of action of SEROQUEL, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL.

SEROQUEL's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of durgs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10-30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin or ketoconazole (See **Drug Interactions** under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION.**)

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam (See **Drug Interactions** under **PRECAUTIONS**).

Clinical Efficacy Data

The efficacy of SEROQUEL in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 to 750 were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

(2) In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

(3) In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

SEROQUEL is indicated for the treatment schizophrenia.

The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION.**)

CONTRAINDICATIONS

SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A pontentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Two possible cases of NMS [2/2387 (0.1%)] have been reported in clinical trials with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrence of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially, or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

PRECAUTIONS

General

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (22/2162) of the patients treated with SEROQUEL, compared with 0% (0/206) on placebo and about 0.5% (2/420) on active control drugs. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (See **DOSAGE AND ADMINISTRATION**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications).

Cataracts: The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular

changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.

Seizures: During clinical trials, seizures occurred in 0.8% (18/2387) of patients treated with SEROQUEL compared to 0.5% (1/206) on placebo and 1% (4/420) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (10/2386) of SEROQUEL patients did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment.

Cholesterol and Triglyceride Elevations: In a pool of 3- to 6-week placebo-controlled trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis.) Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In the 3- to 6-week placebo-controlled trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia and close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal Impairment and Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on SEROQUEL

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION**.)

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine: Administration of muiltiple daily doses up to 75 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery or antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicullar cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS**, General).

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification was detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown.

Continued on next page

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established.

Geriatric Use: Of the approximately 2400 patients in clinical studies with SEROQUEL, 8% (190) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The premarketing development program for SEROQUEL included over 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL. Of these 2600 subjects, approximately 2300 were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 865 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the porportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) of schizophrenia in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 750 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%).

Table 1: Treatment-Emergent Adverse Experience Incidence in 3- to 6-Week Placebo-Controlled Clinical Trials[1]

Body System/ Preferred Term	SEROQUEL (n=510)	Placebo (n=206)
Body as a Whole		
Headache	19%	18%
Asthenia	4%	3%
Abdominal pain	3%	1%
Back pain	2%	1%
Fever	2%	1%
Nervous System		
Somnolence	18%	11%
Dizziness	10%	4%
Digestive System		
Constipation	9%	5%
Dry Mouth	7%	3%
Dyspepsia	6%	2%
Cardiovascular System		
Postural hypotension	7%	2%
Tachycardia	7%	5%
Metabolic and Nutritional Disorders		
Weight gain	2%	0%
Skin and Appendages		
Rash	4%	3%
Respiratory System		
Rhinitis	3%	1%
Special Senses		
Ear pain	1%	0%

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[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: pain, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhea, myalgia, agitation, insomnia, anxiety, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, dry skin, amblyopia and urinary tract infection.

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-Related Adverse Events: Spontaneously elicited adverse event data from a study comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

		SEROQUEL				
Dose Groups	Placebo	75mg	150mg	300mg	600mg	750mg
Parkinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS						
Incidence	16%	6%	6%	4%	8%	6%
Anticholinergic						
Medications	14%	11%	10%	8%	12%	11%

In three additional placebo-controlled clinical trials using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**):

Weight Gain: The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%).

Laboratory Changes: An assessment of the pre-marketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the pre-marketing database of approximately 2200 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Nervous System: ***Frequent:*** hypertonia, dysarthria; ***Infrequent:*** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma.

Body as a Whole: ***Frequent:*** flu syndrome; ***Infrequent:*** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; ***Rare:*** abdomen enlarged.

Digestive System: ***Frequent:*** anorexia; ***Infrequent:*** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; ***Rare:*** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

Cardiovascular System: ***Frequent:*** palpitation; ***Infrequent:*** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: ***Frequent:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation.

Metabolic and Nutritional System: ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: ***Frequent:*** sweating; ***Infrequent:*** pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: ***Infrequent:*** dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: ***Infrequent:*** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: ***Frequent:*** leukopenia; ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia.

Endocrine System: ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism.

*adjusted for gender

Post-Marketing Experience: Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include the following: rarely leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will

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be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human Experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arthythmias. If anti-arrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state for SEROQUEL would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly, and in patients who are debilitated or who have a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients.

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (See Drug Interactions under **PRECAUTIONS**).

Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should remain on it, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on SEROQUEL, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week of SEROQUEL, titration of SEROQUEL is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to SEROQUEL, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, indentified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

300 mg Tablets (NDC 0310-0274) white, capsule-shaped, biconvex; film coated tablets, intagliated with 'SEROQUEL' on one side and '300' on the other side, are supplied in bottles of 60 tablets and hospital unit dose packages of 100 tablets.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

ANIMAL TOXICOLOGY

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2-year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine-treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

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64154-01 Rev 1/01

AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
Made in USA

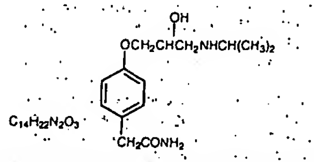
Shown in Product Identification Guide, page 306

TENORMIN® Tablets ℞
TENORMIN® I.V. Injection

[ten-or 'min]
(atenolol)

DESCRIPTION

TENORMIN (atenolol), a synthetic, $beta_1$-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl)amino]propoxy]-. The molecular and structural formulas are:



$C_{14}H_{22}N_2O_3$

Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/ water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN is available as 25, 50 and 100 mg tablets for oral administration. TENORMIN for parenteral administration is available as TENORMIN I.V. Injection containing 5 mg atenolol in 10 mL sterile, isotonic, citrate-buffered, aqueous solution. The pH of the solution is 5.5–6.5.

Inactive Ingredients: TENORMIN Tablets: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. TENORMIN I.V. Injection: Sodium chloride for isotonicity and citric acid and sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

TENORMIN is a $beta_1$-selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, TENORMIN inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Pharmacokinetics and Metabolism: In man, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between two (2) and four (4) hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, TENORMIN undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an intravenous dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. TENORMIN also differs from propranolol in that only a small amount (6%–16%) of atenolol is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a fourfold interpatient variation.

The elimination half-life of oral TENORMIN is approximately 6 to 7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following intravenous administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of TENORMIN is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 $mL/min/1.73m^2$. (See DOSAGE AND ADMINISTRATION).

Pharmacodynamics: In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of TENORMIN has been demonstrated by: (1) reduction in resting and exercise heart rate and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol induced tachycardia, and (4) reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of TENORMIN, as measured by reduction of exercise tachycardia, is apparent within one hour following oral administration of a single dose. This effect is maximal at about 2 to 4 hours, and persists for at least 24 hours. Maximum reduction in exercise tachycardia occurs within 5 minutes of an intravenous dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma TENORMIN concentration. The effect on exercise tachycardia of a single 10 mg intravenous dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 mg and 100 mg is still evident beyond 24 hours following administration. However, as has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma level.

In normal subjects, the $beta_1$-selectivity of TENORMIN has been shown by its reduced ability to reverse the $beta_2$-mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of TENORMIN producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. In a placebo controlled comparison of approximately equipotent oral doses of several beta blockers, TENORMIN produced a significantly smaller decrease of FEV_1 than nonselective beta blockers such as propranolol and, unlike those agents, did not inhibit bronchodilation in response to isoproterenol.

Consistent with its negative chronotropic effect due to beta blockade of the SA node, TENORMIN increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. TENORMIN is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and during exercise.

In controlled clinical trials, TENORMIN, given as a single daily dose, was an effective antihypertensive agent providing 24-hour reduction of blood pressure. TENORMIN has been studied in combination with thiazide-type diuretics, and the blood pressure effects of the combination are approximately additive. TENORMIN is also compatible with methyldopa, hydralazine, and prazosin, each combination

Continued on next page

Reminyl—Cont.

The recommended starting dose of REMINYL® is 4 mg twice a day (8 mg/day). After a minimum of 4 weeks of treatment, if this dose is well tolerated, the dose should be increased to 8 mg twice a day (16 mg/day). A further increase to 12 mg twice a day (24 mg/day) should be attempted only after a minimum of 4 weeks at the previous dose.

REMINYL® should be administered twice a day, preferably with morning and evening meals.

Patients and caregivers should be informed that if therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Caregivers should be instructed in the correct procedure for administering REMINYL® Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering REMINYL® Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

The abrupt withdrawal of REMINYL® in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of REMINYL® are lost, however, when the drug is discontinued.

Doses in Special Populations

Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), the dose should generally not exceed 16 mg/day. The use of REMINYL® in patients with severe hepatic impairment (Child-Pugh score of 10-15) is not recommended.

For patients with moderate renal impairment the dose should generally not exceed 16 mg/day. In patients with severe renal impairment (creatinine clearance < 9 mL/min), the use of REMINYL® is not recommended.

HOW SUPPLIED

REMINYL® (galantamine hydrobromide) tablets are imprinted "JANSSEN" on one side, and "G" and the strength "4", "8", or "12" on the other.

4 mg off-white tablet: bottles of 60 NDC 50458-390-60
8 mg pink tablet: bottles of 60 NDC 50458-391-60
12 mg orange-brown tablet: bottles of 60 NDC 50458-392-60

REMINYL® (galantamine hydrobromide) 4 mg/mL oral solution (NDC 50458-399-10) is a clear colorless solution supplied in 100 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.5 mL, while the maximum calibrated volume is 4 mL.

Storage and Handling

REMINYL® tablets should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

REMINYL® Oral Solution should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. DO NOT FREEZE.

Keep out of reach of children.

7517304
October 2001
US Patent No. 4,663,318

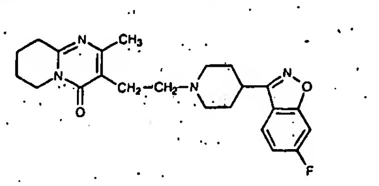
REMINYL® tablets are manufactured by:
Janssen-Cilag SpA
Latina, Italy
REMINYL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium
REMINYL® tablets and oral solution are distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560
Janssen Pharmaceutica Products, L.P.
Shown in Product Identification Guide, page 319

RISPERDAL® ℞

[ris ′pər dăl]
(risperidone)
Tablets/Oral Solution

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide, the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome $P_{450}IID_6$ to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome $P_{450}IID_6$, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome $P_{450}IID_6$ is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5–6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome $P_{450}IID_6$ could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n≈70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome $P_{450}IID_6$. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (See PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 90% over the in vitro concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1-acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 µg/mL), warfarin (10 µg/mL) and carbamazepine (10 µg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

Renal Impairment: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (See DOSAGE AND ADMINISTRATION).

Race and Gender Effects: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2–8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6 to 8-weeks) controlled trials of schizophrenic inpatients (See CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (See Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12–16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2–3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL® treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (See CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism: Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed an infant if they are taking RISPERDAL®.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking RISPERDAL®.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n~70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of

Continued on next page

cytochrome $P_{450}IID_6$. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at which these tumors occurred.

[See table below]

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a mg/m^2 basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m^2 basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL® therapy is unknown.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. It has been demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL® should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (See PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in phase 2–3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL® related adverse event (See PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.8% in active-control patients in the phase 2–3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL®-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1: **Treatment-Emergent Adverse Experience Incidence in 6 to 8-Week Controlled Clinical Trials[1]**

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

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[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≤ 10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (See DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events:

Extrapyramidal symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment. Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkin

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m^2 (mg/kg) LOWEST EFFECT LEVEL	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m^2 (mg/kg) HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 (*9.4*)	0.2 (*2.4*)
Endocrine pancreas adenomas	rat	male	1.5 (*9.4*)	0.4 (*2.4*)
Mammary gland adenocarcinomas	mouse	female	0.2 (*2.4*)	none
	rat	female	0.4 (*2.4*)	none
	rat	male	6 (*37.5*)	1.5 (*9.4*)
Mammary gland neoplasms, Total	rat	male	1.5 (*9.4*)	0.4 (*2.4*)

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23%	19%
26%	20%
20%	9%
8%	1%
3%	1%
34%	16%
12%	12%
7%	1%
13%	3%
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sonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatiguability, and increased pigmentation.

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes: The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6 to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the listings that follow).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-Intestinal Disorders: *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: *Rare:* tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: *Rare:* bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL® overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose: RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early short-term clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent short-term controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. In a long-term controlled trial in stable patients, RISPERDAL® was administered on a QD schedule at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1–2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in short-term clinical trials supporting effectiveness of RISPERDAL®, however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day (See Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to

Continued on next page

Risperdal—Cont.

determine the need for maintenance treatment with appropriate dose.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Dosage in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2–3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°–25°C (59°–77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°–25°C (59°–77°F). Protect from light and freezing.

Keep out of reach of children.

7503220
US Patent 4,804,663
February 2002

RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy
RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium
RISPERDAL® tablets and oral solution are distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

Shown in Product Identification Guide, page 319

SPORANOX ℞

[spər 'ah-nāks"]
(itraconazole)
Capsules

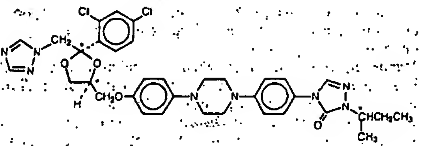
Congestive Heart Failure

SPORANOX® (itraconazole) Capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. If signs or symptoms of congestive heart failure occur during administration of SPORANOX® Capsules, discontinue administration. When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Post-marketing Experience for more information.)

Drug Interactions: Coadministration of cisapride, pimozide, quinidine, or dofetilide with SPORANOX® (itraconazole) Capsules, Injection or Oral Solution is contraindicated. SPORANOX®, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, or quinidine, concomitantly with SPORANOX® and/or other CYP3A4 inhibitors. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.

DESCRIPTION

SPORANOX® is the brand name for itraconazole, a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following structural formula and nomenclature:



(±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2R*,4S*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2 1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2S*,4R*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl] phenyl]-Δ^2-1,2,4-triazolin-5-one

or

(±)-1-[(RS)-sec-butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one

Itraconazole has a molecular formula of $C_{35}H_{38}Cl_{2}N_{8}O_{4}$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

SPORANOX® Capsules contain 100 mg of itraconazole coated on sugar spheres. Inactive ingredients are gelatin, hydroxypropyl methylcellulose, polyethylene glycol (PEG) 20,000, starch, sucrose, titanium dioxide, FD&C Blue No. 1, FD&C Blue No. 2, D&C Red No. 22 and D&C Red No. 28.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism: NOTE: The plasma concentrations reported below were measured by high-performance liquid chromatography (HPLC) specific for itraconazole. When itraconazole in plasma is measured by a bioassay, values reported are approximately 3.3 times higher than those obtained by HPLC due to the presence of the bioactive metabolite, hydroxyitraconazole. (See MICROBIOLOGY.)

The pharmacokinetics of itraconazole after intravenous administration and its absolute oral bioavailability from an oral solution were studied in a randomized crossover study in 6 healthy male volunteers. The observed absolute oral bioavailability of itraconazole was 55%.

The oral bioavailability of itraconazole is maximal when SPORANOX® (itraconazole) Capsules are taken with a full meal. The pharmacokinetics of itraconazole were studied in 6 healthy male volunteers who received, in a crossover design, single 100-mg doses of itraconazole as a polyethylene glycol capsule, with or without a full meal. The same 6 volunteers also received 50 mg or 200 mg with a full meal in a crossover design. In this study, only itraconazole plasma concentrations were measured. The respective pharmacokinetic parameters for itraconazole are presented in the table below:

[See table below]

Doubling the SPORANOX® dose results in approximately a three-fold increase in the itraconazole plasma concentrations.

Values given in the table below represent data from a crossover pharmacokinetics study in which 27 healthy male volunteers each took a single 200-mg dose of SPORANOX® Capsules with or without a full meal:

[See table at top of next page]

Absorption of itraconazole under fasted conditions in individuals with relative or absolute achlorhydria, such as patients with AIDS or volunteers taking gastric acid secretion suppressors (e.g., H_2 receptor antagonists), was increased when SPORANOX® Capsules were administered with a cola beverage. Eighteen men with AIDS received single 200-mg doses of SPORANOX® Capsules under fasted conditions with 8 ounces of water or 8 ounces of a cola beverage in a crossover design. The absorption of itraconazole was increased when SPORANOX® Capsules were coadministered with a cola beverage, with AUC_{0-24} and C_{max} increasing 75% ± 121% and 95% ± 128%, respectively.

Thirty healthy men received single 200-mg doses of SPORANOX® Capsules under fasted conditions either 1) with water; 2) with water, after ranitidine 150 mg b.i.d. for 3 days; or 3) with cola, after ranitidine 150 mg b.i.d. for 3 days. When SPORANOX® Capsules were administered after ranitidine pretreatment, itraconazole was absorbed to a lesser extent than when SPORANOX® Capsules were administered alone, with decreases in AUC_{0-24} and C_{max} of 39% ± 37% and 42% ± 39%, respectively. When SPORANOX® Capsules were administered with cola after ranitidine pretreatment, itraconazole absorption was comparable to that observed when SPORANOX® Capsules were administered alone. (See PRECAUTIONS: Drug Interactions.)

Steady-state concentrations were reached within 15 days following oral doses of 50 mg to 400 mg daily. Values given in the table below are data at steady-state from a pharmacokinetics study in which 27 healthy male volunteers took 200-mg SPORANOX® Capsules b.i.d. (with a full meal) for 15 days:

	Itraconazole	Hydroxyitraconazole
C_{max} (ng/mL)	2282 ± 514*	3488 ± 742
C_{min} (ng/mL)	1855 ± 535	3349 ± 761
T_{max} (hours)	4.6 ± 1.8	3.4 ± 3.4
AUC_{0-12h} (ng•h/mL)	22569 ± 5375	38572 ± 8450
$t_{½}$ (hours)	64 ± 32	56 ± 24

* mean ± standard deviation

The plasma protein binding of itraconazole is 99.8% and that of hydroxyitraconazole is 99.5%. Following intravenous administration, the volume of distribution of itraconazole averaged 796 ± 185 liters.

Itraconazole is metabolized predominately by the cytochrome P450 3A4 isoenzyme system (CYP3A4), resulting in the formation of several metabolites, including hydroxyitraconazole, the major metabolite. Results of a pharmacokinetics study suggest that itraconazole may undergo saturable metabolism with multiple dosing. Fecal excretion of the parent drug varies between 3–18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No single excreted metabolite represents more than 5% of a dose. Itraconazole total plasma clearance averaged 381 ± 95 mL/minute following intravenous administration. (See CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions for more information.)

Special Populations:

Renal Insufficiency: A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a

	50 mg (fed)	100 mg (fed)	100 mg (fasted)	200 mg (fed)
C_{max} (ng/mL)	45 ± 16*	132 ± 67	38 ± 20	289 ± 100
T_{max} (hours)	3.2 ± 1.3	4.0 ± 1.1	3.3 ± 1.0	4.7 ± 1.4
$AUC_{0-\infty}$ (ng•h/mL)	567 ± 264	1899 ± 838	722 ± 289	5211 ± 2116

* mean ± standard deviation

ve RR)	95% CI for RR
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9	0.75, 1.30
1	0.59, 0.85

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10. Avoid exposing Xigris solutions to heat and/or direct sunlight. No incompatibilities have been observed between Xigris and glass infusion bottles or infusion bags and syringes made of polyvinylchloride, polyethylene, polypropylene, or polyolefin.

HOW SUPPLIED

Xigris is available in 5 mg and 20 mg single-use vials containing sterile, preservative-free, lyophilized drotrecogin alfa (activated).

Vials:
5 mg Vials
NDC 0002-7559-01
20 mg Vials
NDC 0002-7561-01

Xigris should be stored in a refrigerator 2° to 8°C (36° to 46°F). Do not freeze. Protect unreconstituted vials of Xigris from light. Retain in carton until time of use. Do not use beyond the expiration date stamped on the vial.

REFERENCES

1. Bernard GR, et al. Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis. *N Engl J Med.* 2001;344:699-709
2. Knaus WA, et al. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13:818–29

Literature issued November 2001
PV 3420 AMP

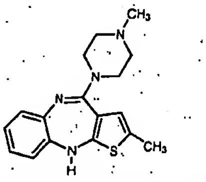
Shown in Product Identification Guide, page 320

ZYPREXA® ℞
[zi-prex-ah]
(Olanzapine) Tablets

ZYPREXA® ZYDIS® ℞
(Olanzapine) Orally Disintegrating Tablets

DESCRIPTION

ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only. Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5.0, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 µmol), 10 mg (32 µmol), 15 mg (48 µmol) or 20 mg (64 µmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ (K_i=4 and 11 nM, respectively), dopamine D_{1-4} (K_i=11-31 nM), muscarinic M_{1-5} (K_i=1.9-25 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β adrenergic receptors (K_i > 10 µM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with Bipolar I Disorder is unknown.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics:

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about one week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (*see* Special Populations).

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1-acid glycoprotein.

Metabolism and Elimination—Following a single oral dose of ^{14}C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Special Populations—

Renal Impairment—Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment—Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Age—In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (>65 years) than in non-elderly subjects (≤65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity (*see* DOSAGE AND ADMINISTRATION).

Gender—Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status—Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race—No specific pharmacokinetic study was conducted to investigate the effects of race. A cross-study comparison between data obtained in Japan and data obtained in the US suggests that exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are administered. Clinical trial safety and efficacy data, however, did not suggest clinically significant differences among Caucasian patients, patients of African descent, and a third pooled category including Asian and Hispanic patients. Dosage modifications for race are, therefore, not recommended.

Combined Effects—The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (*see* DOSAGE AND ADMINISTRATION).

Clinical Efficacy Data:

Schizophrenia

The efficacy of olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the two trials, but this trial did not compare these two drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed but less well evaluated scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which is embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5.0±2.5 mg/day, 10.0±2.5 mg/day, and 15.0±2.5 mg/day) on a once daily schedule, the two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high dose group over the medium dose group.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

Bipolar Mania

The efficacy of olanzapine in the treatment of acute manic episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

INDICATIONS AND USAGE

Schizophrenia

ZYPREXA is indicated for the treatment of schizophrenia.

The efficacy of ZYPREXA was established in short-term (6-week) controlled trials of schizophrenic inpatients (*see* CLINICAL PHARMACOLOGY).

The effectiveness of oral ZYPREXA at maintaining a treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a period of up to 8 months has been demon-

Continued on next page

• Identi-Code® symbol. This product information was prepared in June 2002. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.

strated in a placebo-controlled trial (*see* CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Bipolar Mania

ZYPREXA is indicated for the short-term treatment of acute manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (*see* CLINICAL PHARMACOLOGY).

The effectiveness of ZYPREXA for longer-term use, that is, for more than 4 weeks treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use ZYPREXA for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

ZYPREXA is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia—A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

PRECAUTIONS

General

Orthostatic Hypotension—Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonistic properties. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD (*see* DOSAGE AND ADMINISTRATION). A more gradual titration to the target dose should be considered if hypotension occurs. Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures—During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hyperprolactinemia—As with other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels, and a modest elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Transaminase Elevations—In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. In two of these patients, liver enzymes decreased toward normal despite continued treatment and in two others, enzymes decreased upon discontinuation of olanzapine. In the remaining two patients, one, seropositive for hepatitis C, had persistent enzyme elevation for four months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

Among all 2500 patients in clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Laboratory Tests).

Potential for Cognitive and Motor Impairment—Somnolence was a commonly reported adverse event associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse event was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Body Temperature Regulation—Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Two olanzapine-treated patients (2/407) in two studies in patients with Alzheimer's disease died from aspiration pneumonia during or within 30 days of the termination of the double-blind portion of their respective studies; there were no deaths in the placebo-treated patients. One of these patients had experienced dysphagia prior to the development of aspiration pneumonia. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide—The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness—Clinical experience with olanzapine in patients with certain concomitant systemic illnesses (*see* Renal Impairment and Hepatic Impairment *under* CLINICAL PHARMACOLOGY, Special Populations) is limited.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

In a fixed-dose study of olanzapine (olanzapine at doses of 5, 10, and 15 mg/day) and placebo in nursing home patients (mean age: 83 years, range: 61-97; median Mini-Mental State Examination (MMSE): 5, range: 0-22) having various psychiatric symptoms in association with Alzheimer's disease, the following treatment-emergent adverse events were reported in all (each and every) olanzapine-treated groups at an incidence of either (1) two-fold or more in excess of the placebo-treated group, where at least 1 placebo-treated patient was reported to have experienced the event, or (2) at least 2 cases if no placebo-treated patient was reported to have experienced the event: somnolence, abnormal gait, fever, dehydration, and back pain. The rate of discontinuation in this study for olanzapine was 12% vs 4% with placebo. Discontinuations due to abnormal gait (1% for olanzapine vs 0% for placebo), accidental injury (1% for olanzapine vs 0% for placebo), and somnolence (3% for olanzapine vs 0% for placebo) were considered to be drug related.

Two flexible-dose studies of olanzapine (started at 2.5 mg/day and titrated up to a maximum of 15 mg/day based on investigator judgment; mean modal dose 4.2 mg) and placebo were conducted in Parkinson's disease patients (mean age: 71 years, range: 50-88 years) having drug-induced (dopamine agonist) psychosis. Patients were required to be stable on the lowest dose of anti-Parkinsonian medications deemed necessary clinically to control the motor symptoms of Parkinson's disease upon entry in the studies and to remain on the same anti-Parkinsonian medications and dosages throughout the studies. The following treatment-emergent adverse events were reported in the olanzapine-treated group at an incidence of at least 5% for olanzapine and two-fold or more in excess of the placebo-treated group: worsening of Parkinsonian symptomatology, hallucinations, somnolence, increased salivation, asthenia, and peripheral edema. The rate of discontinuation in these studies due to adverse events for olanzapine was 20% vs 3% with placebo. Discontinuations due to worsening of Parkinsonian symptomatology (8% for olanzapine vs 0% for placebo) were considered to be drug related.

As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia and/or Parkinson's disease (*see* PRECAUTIONS).

Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients (*see* Orthostatic Hypotension).

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe olanzapine:

Orthostatic Hypotension—Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol (*see* Drug Interactions).

Interference with Cognitive and Motor Performance—Because olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Pregnancy—Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with olanzapine.

Nursing—Patients should be advised not to breast-feed an infant if they are taking olanzapine.

Concomitant Medication—Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol—Patients should be advised to avoid alcohol while taking olanzapine.

Heat Exposure and Dehydration—Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

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Phenylketonurics—ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively).

Laboratory Tests—Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Transaminase Elevations).

Drug Interactions—The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents.

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Olanzapine—Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

Charcoal—The administration of activated charcoal (1 g) reduced the Cmax and AUC of olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

Cimetidine and Antacids—Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Carbamazepine—Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Ethanol—Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics.

Fluoxetine—Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

Fluvoxamine—Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Valproate—Studies in vitro using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Warfarin—Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics.

Effect of Olanzapine on Other Drugs—In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam, lithium, ethanol, or biperiden. However, the coadministration of either diazepam or ethanol with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility—

Carcinogenesis—Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily dose on a mg/m^2 basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily dose on a mg/m^2 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily dose on a mg/m^2 basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily dose on a mg/m^2 basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily dose on a mg/m^2 basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily dose on a mg/m^2 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown (*see* Hyperprolactinemia *under* PRECAUTIONS, General).

Mutagenesis—No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility—In a fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily dose on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily dose on a mg/m^2 basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily dose on a mg/m^2 basis); therefore olanzapine may produce a delay in ovulation.

Pregnancy—

Pregnancy Category C—In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily dose on a mg/m^2 basis, respectively) no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily dose on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily dose on a mg/m^2 basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the maximum recommended human daily dose on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery—Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

Nursing Mothers—Olanzapine was excreted in milk of treated rats during lactation. It is not known if olanzapine is excreted in human milk. It is recommended that women receiving olanzapine should not breast-feed.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in patients with various psychiatric symptoms in association with Alzheimer's disease and in Parkinson's disease patients with drug-induced (dopamine agonist) psychosis have suggested that there may be a different tolerability profile in these populations compared to younger patients with schizophrenia. As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia and/or Parkinson's disease. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient (*see* PRECAUTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for olanzapine consisting of 4189 patients with approximately 2665 patient-years of exposure. This database includes: (1) 2500 patients who participated in multiple-dose premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in premarketing bipolar mania trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in a trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; and (4) 1316 patients from 43 additional clinical trials as of May 1, 1997.

The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania. However, this information is also generally applicable to bipolar mania.

Adverse events during exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used initially to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported events do not include those event terms which were so general as to be uninformative. Events listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the events occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

Incidence of Adverse Events in Short-Term, Placebo-Controlled Trials—The following findings are based on the short-term, placebo-controlled premarketing trials for schizophrenia and bipolar mania and a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials—

Schizophrenia—Overall, there was no difference in the incidence of discontinuation due to adverse events (5% for olanzapine vs 6% for placebo). However, discontinuations due to increases in SGPT were considered to be drug related (2% for olanzapine vs 0% for placebo) (*see* PRECAUTIONS).

Bipolar Mania—Overall, there was no difference in the incidence of discontinuation due to adverse events (2% for olanzapine vs 2% for placebo).

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials—The most commonly observed adverse events associated with the use of olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events
Associated with the Use of Olanzapine
in 6-Week Trials - SCHIZOPHRENIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=248)	Placebo (N=118)
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder[1]	8	4
Akathisia	5	1

[1] Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

Continued on next page

• Identi-Code® symbol. This product information was prepared in June 2002. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.

Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 3-Week and 4-Week Trials—BIPOLAR MANIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=125)	Placebo (N=129)
Asthenia	15	6
Dry mouth	22	7
Constipation	11	5
Dyspepsia	11	5
Increased appetite	6	3
Somnolence	35	13
Dizziness	18	6
Tremor	6	3

Adverse Events Occurring at an Incidence of 2% or More Among Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials—

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with olanzapine (doses ≥2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

Table 1

Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Clinical Trials[1]

Body System/Adverse Event	Percentage of Patients Reporting Event: Olanzapine (N=532)	Percentage of Patients Reporting Event: Placebo (N=294)
Body as a Whole		
Accidental Injury	12	8
Asthenia	10	9
Fever	6	2
Back pain	5	2
Chest pain	3	1
Cardiovascular System		
Postural hypotension	3	1
Tachycardia	3	1
Hypertension	2	1
Digestive System		
Dry mouth	9	5
Constipation	9	4
Dyspepsia	7	5
Vomiting	4	3
Increased appetite	3	2
Hemic and Lymphatic System		
Ecchymosis	5	3
Metabolic and Nutritional Disorders		
Weight gain	5	3
Peripheral edema	3	1
Musculoskeletal System		
Extremity pain (other than joint)	5	3
Joint pain	5	3
Nervous System		
Somnolence	29	13
Insomnia	12	11
Dizziness	11	4
Abnormal gait	6	1
Tremor	4	3
Akathisia	3	2
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	6	3
Pharyngitis	4	3
Special Senses		
Amblyopia	3	2
Urogenital System		
Urinary incontinence	2	1
Urinary tract infection	2	1

[1] Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression, diarrhea, dysmenorrhea[2], hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid reaction, personality disorder[3], rash, thinking abnormal, weight loss.

[2] Denominator used was for females only (olanzapine, N=201; placebo, N=114).

[3] Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

Additional Findings Observed in Clinical Trials—The following findings are based on clinical trials.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—

Extrapyramidal Symptoms: The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY RATING SCALES INCIDENCE IN A FIXED DOSAGE RANGE, PLACEBO-CONTROLLED CLINICAL TRIAL—ACUTE PHASE*

	Percentage of Patients			
	Placebo	Olanzapine 5± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism[1]	15	14	12	14
Akathisia[2]	23	16	19	27

* No statistically significant differences.

[1] Percentage of patients with a Simpson-Angus Scale total score >3.

[2] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse events during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY ADVERSE EVENTS INCIDENCE IN A FIXED DOSAGE RANGE, PLACEBO-CONTROLLED CLINICAL TRIAL—ACUTE PHASE

	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Dystonic events[1]	1	3	2	3
Parkinsonism events[2]	10	8	14	20
Akathisia events[3]	1	5	11*	10*
Dyskinetic events[4]	4	0	2	1
Residual events[5]	1	2	5	1
Any extrapyramidal event	16	15	25	32*

* Statistically significantly different from placebo.

[1] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[2] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[3] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[4] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[5] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

Other Adverse Events: The following table addresses dose relatedness for other adverse events using data from a schizophrenia trial involving fixed dosage ranges. It enumerates the percentage of patients with treatment-emergent adverse events for the three fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse events for which there was a statistically significant trend.

	Percentage of Patients Reporting Event			
Adverse Event	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Asthenia	15	8	9	20
Dry mouth	4	3	5	13
Nausea	9	0	2	9
Somnolence	16	20	30	39
Tremor	3	0	5	7

Vital Sign Changes—Olanzapine is associated with orthostatic hypotension and tachycardia (*see* PRECAUTIONS).

Weight Gain—In placebo-controlled, 6-week studies, weight gain was reported in 5.6% of olanzapine patients compared to 0.8% of placebo patients. Olanzapine patients gained an average of 2.8 kg, compared to an average 0.4 kg weight loss in placebo patients; 29% of olanzapine patients gained greater than 7% of their baseline weight, compared to 3% of placebo patients. A categorization of patients at baseline on the basis of body mass index (BMI) revealed a significantly greater effect in patients with low BMI compared to normal or overweight patients; nevertheless, weight gain was greater in all 3 olanzapine groups compared to the placebo group. During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Laboratory Changes—An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in SGPT, SGOT, and GGT (*see* PRECAUTIONS). Olanzapine administration was also associated with increases in serum prolactin (*see* PRECAUTIONS), with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models (*see* ANIMAL TOXICOLOGY), careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

In two clinical trials in schizophrenia patients (n=107) where random triglycerides were measured, 1.9% of olanzapine-treated patients with baseline random triglycerides below the upper limits of normal for fasting triglycerides showed a random triglyceride level greater than two-fold the upper limit of normal for fasting triglycerides, with no patients showing greater than a three-fold increase, at any point during 8 weeks of treatment. This analysis used upper limit of normal reference values for fasting triglycerides since the normal range for random triglyceride values has not been established. Given the large intrasubject variability of random triglyceride levels, the clinical significance of this finding is unclear.

ECG Changes—Between-group cmparisons for pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine use was associated with a mean increase in heart rate of 2.4 beats per minute compared to no change among placebo patients. This slight tendency to tachycardia may be related to olanzapine's potential for inducing orthostatic changes (*see* PRECAUTIONS).

Other Adverse Events Observed During the Clinical Trial Evaluation of Olanzapine—

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with olanzapine (at multiple doses ≥ 1 mg/day) in clinical trials (4189 patients, 2665 patient-years of exposure). This listing does not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole—*Frequent:* dental pain, flu syndrome, intentional injury, and suicide attempt; *Infrequent:* abdomen enlarged, chills, chills and fever, face edema, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, and photosensitivity reaction; *Rare:* hangover effect and sudden death.

Cardiovascular System—*Frequent:* hypotension; *Infrequent:* bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation,

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vasodilatation, and ventricular extrasystoles; *Rare:* arteritis, atrial fibrillation, heart failure, and pulmonary embolus.

Digestive System—*Frequent:* increased salivation and thirst; *Infrequent:* dysphagia, eructation, fecal impaction, fecal incontinence, flatulence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, and tooth caries; *Rare:* aphthous stomatitis, enteritis, esophageal ulcer, esophagitis, glossitis, ileus, intestinal obstruction, liver fatty deposit, and tongue discoloration.

Endocrine System—*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis and goiter.

Hemic and Lymphatic System—*Frequent:* leukopenia; *Infrequent:* anemia, cyanosis, leukocytosis, lymphadenopathy, thrombocythemia, and thrombocytopenia; *Rare:* normocytic anemia.

Metabolic and Nutritional Disorders—*Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema, and water intoxication; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, and ketosis.

Musculoskeletal System—*Frequent:* joint stiffness and twitching; *Infrequent:* arthritis, arthrosis, bursitis, leg cramps, and myasthenia; *Rare:* bone pain, myopathy, osteoporosis, and rheumatoid arthritis.

Nervous System—*Frequent:* abnormal dreams, emotional lability, euphoria, libido decreased, paresthesia, and schizophrenic reaction; *Infrequent:* alcohol misuse, amnesia, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, coma, delirium, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, tobacco misuse, vertigo, and withdrawal syndrome; *Rare:* akinesia, circumoral paresthesia, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, and subarachnoid hemorrhage.

Respiratory System—*Frequent:* dyspnea; *Infrequent:* apnea, aspiration pneumonia, asthma, atelectasis, epistaxis, hemoptysis, hyperventilation, laryngitis, pneumonia, and voice alteration; *Rare:* hiccup, hypoventilation, hypoxia, lung edema, and stridor.

Skin and Appendages—*Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin ulcer, and vesiculobullous rash; *Rare:* hirsutism, pustular rash, skin discoloration, and urticaria.

Special Senses—*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, corneal lesion, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, and tinnitus; *Rare:* glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, and pigment deposits lens.

Urogenital System—*Frequent:* amenorrhea*, hematuria, metrorrhagia*, and vaginitis*; *Infrequent:* abnormal ejaculation*, breast pain, cystitis, decreased menstruation*, dysuria, female lactation, glycosuria, impotence*, increased menstruation*, menorrhagia*, polyuria, premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urination impaired, uterine fibroids enlarged*, and vaginal hemorrhage*; *Rare:* albuminuria, gynecomastia, mastitis, oliguria, and urinary urgency.

*Adjusted for gender.

Postintroduction Reports—Adverse events reported since market introduction which were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, pancreatitis, and priapism.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class—Olanzapine is not a controlled substance.

Physical and Psychological Dependence—In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily dose on a mg/m^2 basis.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience—In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

During the first 2 years of marketing, Eli Lilly and Company received reports of 178 cases of possible or definite overdose with olanzapine alone (at doses up to 1500 mg). Symptoms possibly but not necessarily causally attributable to the overdose were reported in 76% of these cases while 24% of reported cases had no symptoms attributable to overdose. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and one patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, coma, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In one case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

	TABLET STRENGTH					
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Tablet No.	4112	4115	4116	4117	4415	4420
Identification	LILLY 4112	LILLY 4115	LILLY 4116	LILLY 4117	LILLY 4415	LILLY 4420
NDC Codes:						
Bottles 60	NDC-0002-4112-60	NDC-0002-4115-60	NDC-0002-4116-60	NDC-0002-4117-60	NDC-0002-4415-60	NDC-0002-4420-60
Blisters - ID* 100	NDC-0002-4112-33	NDC-0002-4115-33	NDC-0002-4116-33	NDC-0002-4117-33	NDC-0002-4415-33	NDC-0002-4420-33
Bottles 1000	NDC-0002-4112-04	NDC-0002-4115-04	—	NDC-0002-4117-04	NDC-0002-4415-04	NDC-0002-4420-04

*Identi-Dose® (unit dose medication, Lilly)

ZYPREXA ZYDIS Tablets*	TABLET STRENGTH			
	5 mg	10 mg	15 mg	20 mg
Tablet No.	4453	4454	4455	4456
Debossed	5	10	15	20
NDC Codes: Dose Pack 30 (Child-Resistant)	NDC-0002-4453-85	NDC-0002-4454-85	NDC-0002-4455-85	NDC-0002-4456-85

ZYPREXA is a registered trademark of Eli Lilly and Company.
ZYDIS is a registered trademark of R. P. Scherer Corporation.

*ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Scherer DDS Limited, United Kingdom, SN5 8RU.

Overdosage Management—The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Dose—Olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations—The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant Illness and Drug Interactions *under* PRECAUTIONS). When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment—While there is no body of evidence available to answer the question of how long the patient treated with olanzapine should remain on it, the effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (*see* CLINICAL PHARMACOLOGY). Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

Bipolar Mania

Usual Dose—Olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations—*See* Dosing in Special Populations *under* DOSAGE AND ADMINISTRATION, Schizophrenia.

Maintenance Treatment—There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with olanzapine. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of olanzapine in such longer-term treatment (i.e., beyond 3-4 weeks).

Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)—After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

HOW SUPPLIED

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and

Continued on next page

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* **Identi-Code® symbol. This product information was prepared in June 2002. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.**

Zyprexa—Cont.

tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:
[See first table at top of previous page]
ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:
[See second table at top of previous page]
Store at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.
Protect from light and moisture.

ANIMAL TOXICOLOGY

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily dose on a mg/m^2 basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily dose on a mg/m^2 basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily dose on a mg/m^2 basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily dose on a mg/m^2 basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.
Literature revised November, 2001
PV 3395 AMP

Shown in Product Identification Guide, page 320

The Liposome Company, Inc.

Please refer to Elan Biopharmaceuticals for product information.

3M Pharmaceuticals

3M CENTER, BLDG. 275-6W-13
P.O. BOX 33275
ST. PAUL, MN 55144

Commercial Customers:
Orders, Returns, Accounting
(800) 447-4537

Trade and Government:
(800) 328-6523

For Medical Information Contact:
Drug Surveillance & Information
3M Pharmaceuticals
3M Center, Bldg. 275-6W-13
P.O. Box 33275
St. Paul, MN 55144
(800) 328-0255
For Aldara™:
(800) 814-1795
In Emergencies:
(800) 328-0255 (all hours)

Website:
www.3M.com/pharma

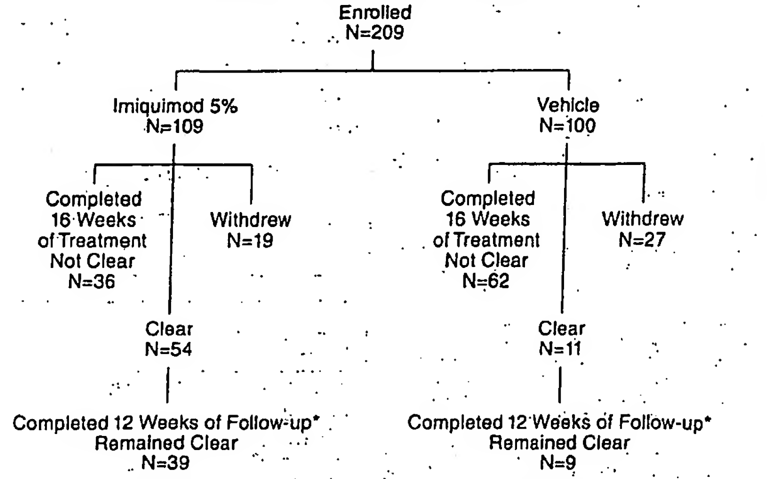
ALDARA™ ℞

[al dar' a]
(imiquimod)
Cream, 5%
For Dermatologic Use Only
Not for Ophthalmic Use

DESCRIPTION

Aldara™ is the brand name for imiquimod which is an immune response modifier. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.

1004-IMIQ – PATIENT ACCOUNTABILITY

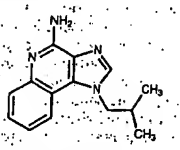


*The other patients were either lost to follow-up or experienced recurrences.

CLEARANCE—STUDY 1004

Treatment	Patients with Complete Clearance of Warts	Patients Without Follow-up	Patients with Warts Remaining at Week 16
Overall			
imiquimod 5% (N =109)	50%	17%	33%
vehicle (N =100)	11%	27%	62%
Females			
imiquimod 5% (N =46)	72%	11%	17%
vehicle (N =40)	20%	33%	48%
Males			
imiquimod 5% (N =63)	33%	22%	44%
vehicle (N =60)	5%	23%	72%

Chemically, imiquimod is 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine. Imiquimod has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3. Its structural formula is:



CLINICAL PHARMACOLOGY

Pharmacodynamics
Imiquimod has no direct antiviral activity in cell culture. A study in 22 patients with genital/perianal warts comparing imiquimod and vehicle shows that imiquimod induces mRNA encoding cytokines including interferon-α at the treatment site. In addition HPVL1 mRNA and HPV DNA are significantly decreased following treatment. However, the clinical relevance of these findings is unknown.
Pharmacokinetics
Percutaneous absorption of [^{14}C] imiquimod was minimal in a study involving 6 healthy subjects treated with a single topical application (5 mg) of [^{14}C] imiquimod cream formulation. No radioactivity was detected in the serum (lower limit of quantitation: 1 ng/mL) and <0.9% of the radiolabelled dose was excreted in the urine and feces following topical application.

CLINICAL STUDIES

In a double-blind, placebo-controlled clinical trial, 209 otherwise healthy patients 18 years of age and older with genital/perianal warts were treated with Aldara 5% cream or vehicle control 3X/week for a maximum of 16 weeks. The median baseline wart area was 69 mm^2 (range 8 to 5525 mm^2). Patient accountability is shown in the figure below.
[See graphic above]
Data on complete clearance are listed in the table below. The median time to complete wart clearance was 10 weeks.
[See table above]

INDICATIONS AND USAGE

Aldara 5% cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in individuals 12 years old and above.

CONTRAINDICATIONS

None known

WARNINGS

Aldara cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and is not recommended for these conditions.

PRECAUTIONS

General
Local skin reactions such as erythema, erosion, excoriation/flaking, and edema are common. Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with Aldara cream can be resumed after the skin reaction has subsided. There is no clinical experience with Aldara cream therapy immediately following the treatment of genital/perianal warts with other cutaneously applied drugs; therefore, Aldara cream administration is not recommended until genital/perianal tissue is healed from any previous drug or surgical treatment. Aldara has the potential to exacerbate inflammatory conditions of the skin.
Information for Patients
Patients using Aldara 5% cream should receive the following information and instructions: The effect of Aldara 5% cream on the transmission of genital/perianal warts is unknown. Aldara 5% cream may weaken condoms and vaginal diaphragms. Therefore, concurrent use is not recommended.

1. This medication is to be used as directed by a physician. It is for external use only. Eye contact should be avoided.
2. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
3. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin.
4. It is recommended that 6–10 hours following Aldara 5% cream application the treatment area be washed with mild soap and water.
5. It is common for patients to experience local skin reactions such as erythema, erosion, excoriation/flaking, and edema at the site of application or surrounding areas. Most skin reactions are mild to moderate. Severe skin reactions can occur and should be reported promptly to the prescribing physician.
6. Some reports have been received of localized hypopigmentation and hyperpigmentation following Aldara use. Follow-up information suggests that these skin color changes may be permanent in some patients.
7. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.
8. Patients should be aware that new warts may develop during therapy, as Aldara is not a cure.

Carcinogenicity, Mutagenesis, and Impairment of Fertility
Rodent carcinogenicity data are not available. Imiquimod was without effect in a series of eight different mutagenicity assays including Ames, mouse lymphoma, CHO chromosome aberration, human lymphocyte chromosome aberration, SHE cell transformation, rat and hamster bone-marrow cytogenetics, and mouse dominant lethal test. Daily oral administration of imiquimod to rats, at doses up to 8 times the recommended human dose on a mg/m^2 basis throughout mating, gestation, parturition and lactation, demonstrated no impairment of reproduction.
Pregnancy
Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Imiquimod was not found to be teratogenic in rat or rabbit teratology studies. In rats at a high maternally toxic dose (28 times human dose on a mg/m^2 basis), reduced pup weights and delayed ossification were observed. In developmental studies with offspring of pregnant rats treated with imiquimod (8 times human dose), no adverse effects were demonstrated.

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Proteus vulgaris
Pseudomonas
Enterobacter
Enterococci

Geocillin is also indicated in the treatment of prostatitis due to susceptible strains of the following organisms:

Escherichia coli
Enterococcus *(S. faecalis)*
Proteus mirabilis
Enterobacter sp.

WHEN HIGH AND RAPID BLOOD AND URINE LEVELS OF ANTIBIOTIC ARE INDICATED, THERAPY WITH GEOPEN (CARBENICILLIN DISODIUM) SHOULD BE INITIATED BY PARENTERAL ADMINISTRATION FOLLOWED, AT THE PHYSICIAN'S DISCRETION, BY ORAL THERAPY.

NOTE: Susceptibility testing should be performed prior to and during the course of therapy to detect the possible emergence of resistant organisms which may develop.

CONTRAINDICATIONS

Geocillin is ordinarily contraindicated in patients who have a known penicillin allergy.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on oral penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with a cephalosporin, and vice versa. Before initiating therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General: As with any penicillin preparation, an allergic response, including anaphylaxis, may occur particularly in a hypersensitive individual.

Long term use of Geocillin may result in the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Since carbenicillin is primarily excreted by the kidney, patients with severe renal impairment (creatinine clearance of less than 10 ml/min) will not achieve therapeutic urine levels of carbenicillin.

In patients with creatinine clearance of 10–20 ml/min it may be necessary to adjust dosage to prevent accumulation of drug.

Laboratory Tests: As with other penicillins, periodic assessment of organ system function including renal, hepatic, and hematopoietic systems is recommended during prolonged therapy.

Drug Interactions: Geocillin (carbenicillin indanyl sodium) blood levels may be increased and prolonged by concurrent administration of probenecid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There are no long-term animal or human studies to evaluate carcinogenic potential. Rats fed 250–1000 mg/kg/day for 18 months developed mild liver pathology (e.g., bile duct hyperplasia) at all dose levels, but there was no evidence of drug-related neoplasia. Geocillin administered at daily doses ranging to 1000 mg/kg had no apparent effect on the fertility or reproductive performance of rats.

Pregnancy Category B: Reproduction studies have been performed at dose levels of 1000 or 500 mg/kg in rats, 200 mg/kg in mice, and at 500 mg/kg in monkeys with no harm to fetus due to Geocillin. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: It is not known whether the use of Geocillin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Carbenicillin class antibiotics are excreted in milk although the amounts excreted are unknown; therefore, caution should be exercised if administered to a nursing woman.

Pediatric Use: Since only limited clinical data is available to date in children, the safety of Geocillin administration in this age group has not yet been established.

ADVERSE REACTIONS

The following adverse reactions have been reported as possibly related to Geocillin administration in controlled studies which include 344 patients receiving Geocillin.

Gastrointestinal: The most frequent adverse reactions associated with Geocillin therapy are related to the gastrointestinal tract. Nausea, bad taste, diarrhea, vomiting, flatulence, and glossitis were reported. Abdominal cramps, dry mouth, furry tongue, rectal bleeding, anorexia, and unspecified epigastric distress were rarely reported.

Dermatologic: Hypersensitivity reactions such as skin rash, urticaria, and less frequently pruritus.

Hematologic: As with other penicillins, anemia, thrombocytopenia, leukopenia, neutropenia, and eosinophilia have infrequently been observed. The clinical significance of these abnormalities is not known.

Miscellaneous: Other reactions rarely reported were hyperthermia, headache, itchy eyes, vaginitis, and loose stools.

Abnormalities of Hepatic Function Tests: Mild SGOT elevations have been observed following Geocillin administration.

OVERDOSAGE

Geocillin is generally nontoxic. Geocillin when taken in excessive amounts may produce mild gastrointestinal irritation. The drug is rapidly excreted in the urine and symptoms are transitory. The usual symptoms of anaphylaxis may occur in hypersensitive individuals.

Carbenicillin blood levels achievable with Geocillin are very low, and toxic reactions as a function of overdosage should not occur systematically. The oral LD_{50} in mice is 3,600 mg/kg, in rats 2,000 mg/kg, and in dogs is in excess of 500 mg/kg. The lethal human dose is not known.

Although never reported, the possibility of accumulation of indanyl should be considered when large amounts of Geocillin are ingested. Free indole, which is a phenol derivative, may be potentially toxic. In general 8–15 grams of phenol, and presumably a similar amount of indole, are required orally before toxicity (peripheral vascular collapse) may occur. The metabolic by-products of indole are nontoxic. In patients with hepatic failure it may be possible for unmetabolized indole to accumulate.

The metabolic by-products of Geocillin, indanyl sulfate and glucuronide, as well as free carbenicillin, are dialyzable.

DOSAGE AND ADMINISTRATION

Geocillin is available as a coated tablet to be administered orally.

Usual Adult Dose

URINARY TRACT INFECTIONS	
Escherichia coli, Proteus species, and *Enterobacter*	1–2 tablets 4 times daily
Pseudomonas and *Enterococcus*	2 tablets 4 times daily
PROSTATITIS	
Escherichia coli, Proteus mirabilis, Enterobacter and *Enterococcus*	2 tablets 4 times daily

HOW SUPPLIED

Geocillin is available as film-coated tablets in bottles of 100's (NDC 0049-1430-66), and unit-dose packages of 100 (10 × 10's) (NDC 0049-1430-41). Each tablet contains carbenicillin indanyl sodium equivalent to 382 mg of carbenicillin.

Revised Sept. 1991 69-1970-00-2

		Mean Urine Concentration of Carbenicillin mcg/ml Hours After Initial Dose		
DRUG	DOSE	0–3	3–6	6–24
Geocillin	1 tablet q.6 hr	1130	352	292
Geocillin	2 tablets q.6 hr	1428	789	809

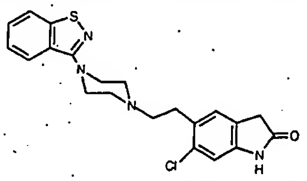
Mean serum concentrations of carbenicillin in this study for these dosages are:

		Mean Serum Concentration mcg/ml Hours After Initial Dose								
DRUG	DOSE	½	1	2	4	6	24	25	26	28
Geocillin	1 tablet q.6 hr	5.1	6.5	3.2	1.9	0.0	0.4	8.8	5.4	0.4
Geocillin	2 tablets q.6 hr	6.1	9.6	7.9	2.6	0.4	0.8	13.2	12.8	3.8

GEODON® ℞
(ziprasidone HCl)
GEODON® for Injection
(ziprasidone mesylate)
FOR IM USE ONLY

DESCRIPTION

GEODON® is available as GEODON Capsules (ziprasidone hydrochloride) for oral administration and as GEODON for Injection (ziprasidone mesylate) for intramuscular injection. Ziprasidone is an antipsychotic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one. The empirical formula of $C_{21}H_{21}ClN_4OS$ (free base of ziprasidone) represents the following structural formula:



GEODON Capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \bullet HCl \bullet H_2O$ and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powder.

GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. GEODON Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

GEODON for Injection contains a lyophilized form of ziprasidone mesylate trihydrate. Chemically, ziprasidone mesylate trihydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, methanesulfonate, trihydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \bullet CH_3SO_3H \bullet 3H_2O$ and its molecular weight is 563.09.

GEODON for Injection is available in a single dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions - see **Preparation for Administration**) for intramuscular administration. Each mL of ziprasidone mesylate for injection (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$, $5HT_{1D}$, and α_1-adrenergic receptors (K_is of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively), and moderate affinity for the histamine H_1 receptor (K_i=47 nM). Ziprasidone functioned as an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and as an agonist at the $5HT_{1A}$ receptor. Ziprasidone inhibited synaptic reuptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC_{50} >1 µM).

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone.

Ziprasidone's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

Ziprasidone's antagonism of α_1-adrenergic receptors may explain the orthostatic hypotension observed with this drug.

Oral Pharmacokinetics

Ziprasidone's activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of ziprasidone are dose-proportional within the proposed clinical dose range, and ziprasidone accumulation is predictable with multiple dosing. Elimination of ziprasidone is mainly via hepatic metabolism with a mean terminal half-life of about 7 hours within the proposed clinical dose range. Steady-state concentrations are achieved within one to three days of dosing. The mean apparent systemic clearance is 7.5 mL/min/kg. Ziprasidone is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Ziprasidone is well absorbed after oral administration, reaching peak plasma concentrations in 6 to 8 hours. The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%. The absorption of ziprasidone is increased up to two-fold in the presence of food.

Distribution: Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to

Continued on next page

plasma proteins, binding primarily to albumin and α_1-acid glycoprotein. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is minimal.

Metabolism and Elimination: Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole (BITP) sulphoxide, BITP-sulphone, ziprasidone sulphoxide, and S-methyl-dihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum. *In vitro* studies using human liver subcellular fractions indicate that S-methyl-dihydroziprasidone is generated in two steps. The data indicate that the reduction reaction is mediated by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on *in vivo* abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

Intramuscular Pharmacokinetics

Systemic Bioavailability: The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 60 minutes post-dose or earlier and the mean half-life ($T_{1/2}$) ranges from two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Metabolism and Elimination: Although the metabolism and elimination of IM ziprasidone have not been systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

Special Populations

Age and Gender Effects—In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between men and women or between elderly (>65 years) and young (18 to 45 years) subjects. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant age or gender-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for age or gender are, therefore, not recommended.

Ziprasidone intramuscular has not been systematically evaluated in elderly patients (65 years and over).

Race—No specific pharmacokinetic study was conducted to investigate the effects of race. Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for race are, therefore, not recommended.

Smoking—Based on *in vitro* studies utilizing human liver enzymes, ziprasidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of ziprasidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any significant pharmacokinetic differences between smokers and nonsmokers.

Renal Impairment—Because ziprasidone is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. The pharmacokinetics of ziprasidone following 8 days of 20 mg BID dosing were similar among subjects with varying degrees of renal impairment (n=27), and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required. Ziprasidone is not removed by hemodialysis.

Hepatic Impairment—As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone; a multiple-dose study at 20 mg BID for 5 days in subjects (n=13) with clinically significant (Childs-Pugh Class A and B) cirrhosis revealed an increase in AUC_{0-12} of 13% and 34% in Childs-Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

Intramuscular ziprasidone has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function.

Drug-Drug Interactions

An *in vitro* enzyme inhibition study utilizing human liver microsomes showed that ziprasidone had little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and thus would not likely interfere with the metabolism of drugs primarily metabolized by these enzymes. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of dextromethorphan, estrogen, progesterone, or lithium (see **Drug Interactions** under **PRECAUTIONS**).

In vivo studies have revealed an approximately 35% decrease in ziprasidone AUC by concomitantly administered carbamazepine, an approximately 35–40% increase in ziprasidone AUC by concomitantly administered ketoconazole, but no effect on ziprasidone's pharmacokinetics by cimetidine or antacid (see **Drug Interactions** under **PRECAUTIONS**).

Clinical Trials

The efficacy of oral ziprasidone in the treatment of schizophrenia was evaluated in 5 placebo-controlled studies, 4 short-term (4- and 6-week) trials and one long-term (52-week) trial. All trials were in inpatients, most of whom met DSM III-R criteria for schizophrenia. Each study included 2 to 3 fixed doses of ziprasidone as well as placebo. Four of the 5 trials were able to distinguish ziprasidone from placebo; one short-term study did not. Although a single fixed-dose haloperidol arm was included as a comparative treatment in one of the three short-term trials, this single study was inadequate to provide a reliable and valid comparison of ziprasidone and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies. The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) are both multi-item inventories of general psychopathology usually used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second widely used assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS) was employed for assessing negative symptoms in one trial.

The results of the oral ziprasidone trials follow:

(1) In a 4-week, placebo-controlled trial (n=139) comparing 2 fixed doses of ziprasidone (20 and 60 mg BID) with placebo, only the 60 mg BID dose was superior to placebo on the BPRS total score and the CGI severity score. This higher dose group was not superior to placebo on the BPRS psychosis cluster or on the SANS.

(2) In a 6-week, placebo-controlled trial (n=302) comparing 2 fixed doses of ziprasidone (40 and 80 mg BID) with placebo, both dose groups were superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score and the PANSS total and negative subscale scores. Although 80 mg BID had a numerically greater effect than 40 mg BID, the difference was not statistically significant.

(3) In a 6-week, placebo-controlled trial (n=419) comparing 3 fixed doses of ziprasidone (20, 60, and 100 mg BID) with placebo, all three dose groups were superior to placebo on the PANSS total score, the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. Only the 100 mg BID dose group was superior to placebo on the PANSS negative subscale score. There was no clear evidence for a dose-response relationship within the 20 mg BID to 100 mg BID dose range.

(4) In a 4-week, placebo-controlled trial (n=200) comparing 3 fixed doses of ziprasidone (5, 20, and 40 mg BID), none of the dose groups was statistically superior to placebo on any outcome of interest.

(5) A study was conducted in chronic, symptomatically stable schizophrenic inpatients (n=294) randomized to 3 fixed doses of ziprasidone (20, 40, or 80 mg BID) or placebo and followed for 52 weeks. Patients were observed for "impending psychotic relapse," defined as CGI-improvement score of ≥6 (much worse or very much worse) and/or scores ≥6 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days. Ziprasidone was significantly superior to placebo in both time to relapse and rate of relapse, with no significant difference between the different dose groups.

There were insufficient data to examine population subsets based on age and race. Examination of population subsets based on gender did not reveal any differential responsiveness.

The efficacy of intramuscular ziprasidone in the management of agitated schizophrenic patients was established in two short-term, double-blind trials of schizophrenic subjects who were considered by the investigators to be "acutely agitated" and in need of IM antipsychotic medication. In addition, patients were required to have a score of 3 or more on at least 3 of the following items of the PANSS: anxiety, tension, hostility and excitement. Efficacy was evaluated by analysis of the area under the curve (AUC) of the Behavioural Activity Rating Scale (BARS) and Clinical Global Impression (CGI) severity rating. The BARS is a seven point scale with scores ranging from 1 (difficult or unable to rouse) to 7 (violent, requires restraint). Patients' scores on the BARS at baseline were mostly 5 (signs of overt activity [physical or verbal], calms down with instructions) and as determined by investigators, exhibited a degree of agitation that warranted intramuscular therapy. There were few patients with a rating higher than 5 on the BARS, as the most severely agitated patients were generally unable to provide informed consent for participation in pre-marketing clinical trials.

Both studies compared higher doses of ziprasidone intramuscular with a 2 mg control dose. In one study, the higher dose was 20 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 4 hours. In the other study, the higher dose was 10 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 2 hours.

The results of the intramuscular ziprasidone trials follow:

(1) In a one-day, double-blind, randomized trial (n=79) involving doses of ziprasidone intramuscular of 20 mg or 2 mg, up to QID, ziprasidone intramuscular 20 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 4 hours, and by CGI severity at 4 hours and study endpoint.

(2) In another one-day, double-blind, randomized trial (n=117) involving doses of ziprasidone intramuscular of 10 mg or 2 mg, up to QID, ziprasidone intramuscular 10 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 2 hours, but not by CGI severity.

INDICATIONS AND USAGE

Ziprasidone is indicated for the treatment of schizophrenia. When deciding among the alternative treatments available for this condition, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs (see **WARNINGS**). Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether ziprasidone will cause torsade de pointes or increase the rate of sudden death is not yet known (see **WARNINGS**).

The efficacy of oral ziprasidone was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY**).

In a placebo-controlled trial involving the follow-up for up to 52 weeks of stable schizophrenic inpatients, GEODON was demonstrated to delay the time to and rate of relapse. The physician who elects to use GEODON for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Ziprasidone intramuscular is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Schizophrenic patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation. The efficacy of intramuscular ziprasidone for acute agitation in schizophrenia was established in single-day controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY**). Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

CONTRAINDICATIONS

QT Prolongation

Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**).

Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with dofetilide, sotalol, quinidine, other Class Ia and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus. Ziprasidone is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**).

Hypersensitivity

Ziprasidone is contraindicated in individuals with a known hypersensitivity to the product.

WARNINGS

QT Prolongation and Risk of Sudden Death

Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QTc interval (see CONTRAINDICATIONS, and see Drug Interactions under PRECAUTIONS). Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS).

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the

treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was co-administered with an inhibitor of the CYP4503A4 metabolism of the drug.

In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine.

In the second phase of the study, the effect of ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg BID).

In placebo-controlled trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg.

In clinical trials with oral ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. One patient had a history of prolonged QTc and a screening measurement of 489 msec; QTc was 503 msec during ziprasidone treatment. The other patient had a QTc of 391 msec at the end of treatment with ziprasidone and upon switching to thioridazine experienced QTc measurements of 518 and 593 msec.

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of ziprasidone at recommended doses in premarketing studies, experience is too limited to rule out an increased risk.

A study evaluating the QT/QTc prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QTc from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patients had a QTc interval exceeding 500 msec.

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, ziprasidone's larger prolongation of QTc length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products (see INDICATIONS AND USAGE).

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistently prolonged QTc intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

For patients taking ziprasidone who experience symptoms that could indicate the occurrence of torsade de pointes, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, e.g., Holter monitoring may be useful.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ziprasidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. However, some patients may require treatment with ziprasidone despite the presence of the syndrome.

PRECAUTIONS

General

Rash—In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these events were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued.

Orthostatic Hypotension—Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with ziprasidone.

Ziprasidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures—During clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hyperprolactinemia—As with other drugs that antagonize dopamine D_2 receptors, ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment—Somnolence was a commonly reported adverse event in patients treated with ziprasidone. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that ziprasidone therapy does not affect them adversely.

Priapism—One case of priapism was reported in the premarketing database. While the relationship of the event to ziprasidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that ziprasidone may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation—Although not reported with ziprasidone in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ziprasidone for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide—The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness—Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses (see **Renal Impairment** and **Hepatic Impairment** under CLINICAL PHARMACOLOGY, **Special Populations**) is limited.

Ziprasidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QTc prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients (see **QTc Prolongation** under WARNINGS and **Orthostatic Hypotension** under PRECAUTIONS).

Information for Patients

Please refer to the patient package insert. To assure safe and effective use of GEODON, the information and instructions provided in the patient information should be discussed with patients.

Laboratory Tests

Patients being considered for ziprasidone treatment that are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before proceeding with treatment. Patients who are

Continued on next page

started on diuretics during ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec (see **WARNINGS**).

Drug Interactions

Drug-drug interactions can be pharmacodynamic (combined pharmacologic effects) or pharmacokinetic (alteration of plasma levels). The risks of using ziprasidone in combination with other drugs have been evaluated as described below. All interactions studies have been conducted with oral ziprasidone. Based upon the pharmacodynamic and pharmacokinetic profile of ziprasidone, possible interactions could be anticipated:

Pharmacodynamic Interactions

(1) Ziprasidone should not be used with any drug that prolongs the QT interval (see **CONTRAINDICATIONS**).
(2) Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs.
(3) Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents.
(4) Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

Pharmacokinetic Interactions

The Effect of Other Drugs on Ziprasidone

Carbamazepine—Carbamazepine is an inducer of CYP3A4; administration of 200 mg BID for 21 days resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.

Ketoconazole—Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg QD for 5 days, increased the AUC and Cmax of ziprasidone by about 35–40%. Other inhibitors of CYP3A4 would be expected to have similar effects.

Cimetidine—Cimetidine at a dose of 800 mg QD for 2 days did not affect ziprasidone pharmacokinetics.

Antacid—The coadministration of 30 mL of Maalox® with ziprasidone did not affect the pharmacokinetics of ziprasidone.

In addition, population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam.

Effect of Ziprasidone on Other Drugs

In vitro studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Lithium—Ziprasidone at a dose of 40 mg BID administered concomitantly with lithium at a dose of 450 mg BID for 7 days did not affect the steady-state level or renal clearance of lithium.

Oral Contraceptives—Ziprasidone at a dose of 20 mg BID did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg).

Dextromethorphan—Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis—Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months in the diet at doses of 2, 6, or 12 mg/kg/day to rats, and 50, 100, or 200 mg/kg/day to mice (0.1 to 0.6 and 1 to 5 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 basis, respectively). In the rat study, there was no evidence of an increased incidence of tumors compared to controls. In male mice, there was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested (50 to 200 mg/kg/day or 1 to 5 times the MRHD on a mg/m^2 basis). Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice at 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD on a mg/m^2 basis). Ziprasidone had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see **Hyperprolactinemia** under **PRECAUTIONS, General**).

Mutagenesis—Ziprasidone was tested in the Ames bacterial mutation assay, the *in vitro* mammalian cell gene mutation mouse lymphoma assay, the *in vitro* chromosomal aberration assay in human lymphocytes, and the *in vivo* chromosomal aberration assay in mouse bone marrow. There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes.

Impairment of Fertility—Ziprasidone was shown to increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis) were mated with untreated females. In a 6-month study in male rats given 200 mg/kg/day (10 times the MRHD on a mg/m^2 basis) there were no treatment-related findings observed in the testes.

Pregnancy—Pregnancy Category C—In animal studies ziprasidone demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses. When ziprasidone was administered to pregnant rabbits during the period of organogenesis, an increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) was observed at a dose of 30 mg/kg/day (3 times the MRHD of 200 mg/day on a mg/m^2 basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD on a mg/m^2 basis) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg/day (2 and 8 times the MRHD on a mg/m^2 basis) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis).

There was an increase in the number of pups born dead and a decrease in postnatal survival through the first 4 days of lactation among the offspring of female rats treated during gestation and lactation with doses of 10 mg/kg/day (0.5 times the MRHD on a mg/m^2 basis) or greater. Offspring developmental delays and neurobehavioral functional impairment were observed at doses of 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis) or greater. A no-effect level was not established for these effects.

There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery—The effect of ziprasidone on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether, and if so in what amount, ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breast feed.

Pediatric Use—The safety and effectiveness of ziprasidone in pediatric patients have not been established.

Geriatric Use—Of the approximately 4500 patients treated with ziprasidone in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability of ziprasidone or for reduced clearance of ziprasidone in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

ADVERSE REACTIONS

The premarketing development program for oral ziprasidone included over 5400 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5400 subjects, over 4500 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1733 patient years. The conditions and duration of treatment with ziprasidone included open-label and double-blind studies, inpatient and outpatient studies, and short-term and longer-term exposure. The premarketing development program for intramuscular ziprasidone included 570 patients and/or normal subjects who received one or more injections of ziprasidone. Over 325 of these subjects participated in trials involving the administration of multiple doses.

Adverse events during exposure were obtained by collecting voluntarily reported adverse experiences, as well as results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Oral Ziprasidone

The following findings are based on a pool of two 6-week and two 4-week placebo-controlled trials in which ziprasidone was administered in doses ranging from 10 to 200 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Oral Ziprasidone

Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients (see **PRECAUTIONS**).

Adverse Events Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term, Oral, Placebo-Controlled Trials

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) in predominantly schizophrenic patients, including only those events that occurred in 1% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

In these studies, the most commonly observed adverse events associated with the use of ziprasidone (incidence of 5% or greater) and observed at a rate on ziprasidone at least twice that of placebo were somnolence (14%), extrapyramidal syndrome (5%), and respiratory disorder (8%).

Table 1. Treatment-Emergent Adverse Event Incidence In Short-Term Oral Placebo-Controlled Trials

	Percentage of Patients Reporting Event	
Body System/Adverse Event	Ziprasidone (N=702)	Placebo (N=273)
Body as a Whole		
Asthenia	5	3
Accidental Injury	4	2
Cardiovascular		
Tachycardia	2	1
Postural Hypotension	1	0
Digestive		
Nausea	10	7
Constipation	9	8
Dyspepsia	8	7
Diarrhea	5	4
Dry Mouth	4	2
Anorexia	2	1
Musculoskeletal		
Myalgia	1	0
Nervous		
Somnolence	14	7
Akathisia	8	7
Dizziness	8	6
Extrapyramidal Syndrome	5	1
Dystonia	4	2
Hypertonia	3	2
Respiratory		
Respiratory Disorder*	8	3
Rhinitis	4	2
Cough Increased	3	1

Skin and Appendages		
Rash	4	3
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	3	2

• Cold symptoms and upper respiratory infection account for >90% of investigator terms pointing to "respiratory disorder".

TABLE 2. Treatment-Emergent Adverse Event Incidence In Short-Term Fixed-Dose Intramuscular Trials

	Percentage of Patients Reporting Event		
Body System/Adverse Event	Ziprasidone 2 mg (N=92)	Ziprasidone 10 mg (N=63)	Ziprasidone 20 mg (N=41)
Body as a Whole			
Headache	3	13	5
Injection Site Pain	9	8	7
Asthenia	2	0	0
Abdominal Pain	0	2	0
Flu Syndrome	1	0	0
Back Pain	1	0	0
Cardiovascular			
Postural Hypotension	0	0	5
Hypertension	2	0	0
Bradycardia	0	0	2
Vasodilation	1	0	0
Digestive			
Nausea	4	8	12
Rectal Hemorrhage	0	0	2
Diarrhea	3	3	0
Vomiting	0	3	0
Dyspepsia	1	3	2
Anorexia	0	2	0
Constipation	0	0	2
Tooth Disorder	1	0	0
Dry Mouth	1	0	0
Nervous			
Dizziness	3	3	10
Anxiety	2	0	0
Insomnia	3	0	0
Somnolence	8	8	20
Akathisia	0	2	0
Agitation	2	2	0
Extrapyramidal Syndrome	2	0	0
Hypertonia	1	0	0
Cogwheel Rigidity	1	0	0
Paresthesia	0	2	0
Personality Disorder	0	2	0
Psychosis	1	0	0
Speech Disorder	0	2	0
Respiratory			
Rhinitis	1	0	0
Skin and Appendages			
Furunculosis	0	2	0
Sweating	0	0	2
Urogenital			
Dysmenorrhea	0	2	0
Priapism	1	0	0

Explorations for interactions on the basis of gender did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of this demographic factor.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

An analysis for dose response in this 4-study pool revealed an apparent relation of adverse event to dose for the following events: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision.

Extrapyramidal Symptoms (EPS)—The incidence of reported EPS for ziprasidone-treated patients in the short-term, placebo-controlled trials was 5% vs. 1% for placebo. Objectively collected data from those trials on the Simpson Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo.

Vital Sign Changes—Ziprasidone is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain—The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 4- and 6- week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. In this set of clinical trials, weight gain was reported as an adverse event in 0.4% and 0.4% of ziprasidone and placebo patients, respectively. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (>7% of body weight) in patients with low BMI (<23) compared to normal (23–27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients who entered the program with a "high" BMI.

ECG Changes—Ziprasidone is associated with an increase in the QTc interval (see **WARNINGS**). Ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients.

Other Adverse Events Observed During the Premarketing Evaluation of Oral Ziprasidone

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with ziprasidone at multiple doses >4 mg/day within the database of 3834 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those event terms that were so general as to be uninformative, events reported only once and that did not have a substantial probability of being acutely life-threatening, events that are part of the illness being treated or are otherwise common as background events, and events considered unlikely to be drug-related. It is important to emphasize that, although the events reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident.

Cardiovascular System: *Frequent:* hypertension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis.

Digestive System: *Frequent:* vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena.

Endocrine: *Rare:* hypothyroidism, hyperthyroidism, thyroiditis.

Hemic and Lymphatic System: *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia.

Metabolic and Nutritional Disorders: *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis.

Musculoskeletal System: *Infrequent:* tenosynovitis; *Rare:* myopathy.

Nervous System: *Frequent:* agitation, tremor, dyskinesia, hostility, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, aki-

Continued on next page

Geodon—Cont.

nesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus.
Respiratory System: *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus.
Skin and Appendages: *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash.
Special Senses: *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis.
Urogenital System: *Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage.

Adverse Findings Observed in Trials of Intramuscular Ziprasidone

Adverse Events Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term Trials of Intramuscular Ziprasidone

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy with intramuscular ziprasidone in 1% or more of patients.

In these studies, the most commonly observed adverse events associated with the use of intramuscular ziprasidone (incidence of 5% or greater) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%).
[See table at top of previous page]

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class—Ziprasidone is not a controlled substance.

Physical and Psychological Dependence—Ziprasidone has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which ziprasidone will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ziprasidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience—In premarketing trials involving more than 5400 patients and/or normal subjects, accidental or intentional overdosage of oral ziprasidone was documented in 10 patients. All of these patients survived without sequelae. In the patient taking the largest confirmed amount, 3240 mg, the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

Management of Overdosage—In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Intravenous access should be established and gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects that might be additive to those of ziprasidone.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, epinephrine and dopamine should not be used, since beta stimulation combined with α_1 antagonism associated with ziprasidone may worsen hypotension. Similarly, it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of ziprasidone, resulting in problematic hypotension.

In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. There is no specific antidote to ziprasidone, and it is not dialyzable. The possibility of multiple drug involvement should be considered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

When deciding among the alternative treatments available for schizophrenia, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs (see **WARNINGS**).

Initial Treatment

GEODON® Capsules should be administered at an initial daily dose of 20 mg BID with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg BID. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, ordinarily patients should be observed for improvement for several weeks before upward dosage adjustment.

GEODON® Capsules

Package Configuration	Capsule Strength (mg)	NDC Code	Imprint
Bottles of 60	20	NDC-0049-3960-60	396
Bottles of 60	40	NDC-0049-3970-60	397
Bottles of 60	60	NDC-0049-3980-60	398
Bottles of 60	80	NDC-0049-3990-60	399
Unit dose/80	20	NDC-0049-3960-41	396
Unit dose/80	40	NDC-0049-3970-41	397
Unit dose/80	60	NDC-0049-3980-41	398
Unit dose/80	80	NDC-0049-3990-41	399

Efficacy in schizophrenia was demonstrated in a dose range of 20 to 100 mg BID in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 to 80 mg BID, but results were not consistent. An increase to a dose greater than 80 mg BID is not generally recommended. The safety of doses above 100 mg BID has not been systematically evaluated in clinical trials.

Maintenance Treatment

While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, systematic evaluation of ziprasidone has shown that its efficacy in schizophrenia is maintained for periods of up to 52 weeks at a dose of 20 to 80 mg BID (see **CLINICAL PHARMACOLOGY**). No additional benefit was demonstrated for doses above 20 mg BID. Patients should be periodically reassessed to determine the need for maintenance treatment.

Intramuscular Administration

The recommended dose is 10 to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied.

If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible.

Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

Dosing in Special Populations

Oral: Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment.

Intramuscular: Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race.

Preparation for Administration

GEODON® for Injection (ziprasidone mesylate) should only be administered by intramuscular injection. Single-dose vials require reconstitution prior to administration; any unused portion should be discarded.

Add 1.2 mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injection.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

GEODON® Capsules are differentiated by capsule color/size and are imprinted in black ink with "Pfizer" and a unique number. GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:
[See table above]

Storage and Handling—GEODON® Capsules should be stored at controlled room temperature, 15°–30°C (59°–86°F).

GEODON® for Injection is available in a single dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions—see **Preparation for Administration**) for intramuscular administration. Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

GEODON® for Injection

Package	Concentration	NDC Code
Single Use Vials	20 mg/mL	NDC-0049-3920-83

Storage and Handling—GEODON® for Injection should be stored at controlled room temperature, 15°–30°C (59°–86°F) in dry form. Protect from light. Following reconstitution, GEODON® for Injection can be stored, when protected from light, for up to 24 hours at 15°–30°C (59°–86°F) or up to 7 days refrigerated, 2°–8°C (36°–46°F).

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69-5770-00-4 Revised July 2002

Shown in Product Identification Guide, page 329

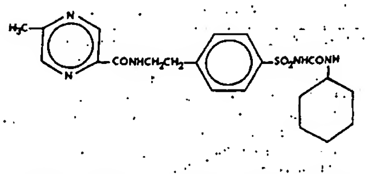
GLUCOTROL® ℞

[glū ′kă-trōl]
(glipizide)
TABLETS
For Oral Use

DESCRIPTION

GLUCOTROL (glipizide) is an oral blood-glucose-lowering drug of the sulfonylurea class.

The Chemical Abstracts name of glipizide is 1-cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido)ethyl]phenyl] sulfonyl]urea. The molecular formula is $C_{21}H_{27}N_5O_4S$; the molecular weight is 445.55; the structural formula is shown below:



Glipizide is a whitish, odorless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 *N* NaOH; it is freely soluble in dimethylformamide. GLUCOTROL tablets for oral use are available in 5 and 10 mg strengths.

Inert ingredients are: colloidal silicon dioxide; lactose; microcrystalline cellulose; starch; stearic acid.

CLINICAL PHARMACOLOGY

Mechanism of Action: The primary mode of action of GLUCOTROL in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets. In humans GLUCOTROL appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which GLUCOTROL lowers blood glucose during long-term administration has not been clearly established. In man, stimulation of insulin secretion by GLUCOTROL in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term GLUCOTROL administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after an oral dose of GLUCOTROL in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

PDR®

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ISBN: 1-56363-526-7

HalfLytely & Bisacodyl—Cont.

testinal obstruction, gastric retention, bowel perforation, toxic colitis or toxic megacolon.

WARNINGS

Flavor Packs are for use only in combination with the contents of the accompanying 2 liter container. No additional ingredients, e.g. flavorings, should be added to the solution. HalfLytely and Bisacodyl Tablets Bowel Prep Kit should be used with caution in patients with severe ulcerative colitis. Do NOT chew or crush the bisacodyl delayed release tablets.

PRECAUTIONS

General: Patients with impaired gag reflex and patients prone to regurgitation or aspiration should be observed during the administration of the solution. If a patient experiences severe bloating, distention or abdominal pain, administration of the solution should be slowed or temporarily discontinued until the symptoms abate. If gastrointestinal obstruction or perforation is suspected, appropriate studies should be performed to rule out these conditions before administration of HalfLytely and Bisacodyl Tablets Bowel Prep Kit.

Patients should avoid consumption of large quantities of water during or after preparation or colonoscopy. Patients with impaired water handling (renal insufficiency or patients taking diuretics) that experience severe vomiting or nausea should be closely monitored including measurement of electrolytes.

Information for patients: HalfLytely and Bisacodyl Tablets Bowel Prep Kit produces a watery stool which cleanses the bowel before examination. Prepare the solution according to the instructions on the kit. For best results, no solid food or milk (clear liquids only) should be consumed on the day of the preparation. No antacids should be taken within one hour of taking the bisacodyl delayed release tablets.

Adults swallow all four bisacodyl delayed release tablets with water (do **NOT** chew or crush). The first bowel movement should occur in approximately 1-6 hours after taking the bisacodyl delayed release tablets. Wait for a bowel movement (or maximum of 6 hours) then drink the solution, 1 (8 oz) glass every 10 minutes (approximately 8 glasses). **Drink ALL of the solution.** Rapid drinking of each portion is better than drinking small amounts continuously. A watery bowel movement should occur in approximately 1 hour after drinking the solution. You may experience some abdominal bloating and distention before the bowels start to move. If severe discomfort or distention occurs, stop drinking the solution temporarily or drink each portion at longer intervals until these symptoms disappear.

Drug Interactions: Oral medication administered within one hour of the start of administration of the solution may be flushed from the gastrointestinal tract and not absorbed. Do not take the bisacodyl delayed release tablets within one hour of taking an antacid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of HalfLytely and Bisacodyl Tablets Bowel Prep Kit. Studies to evaluate its potential for impairment of fertility or its mutagenic potential have not been performed.

Pregnancy: Category C. Animal reproduction studies have not been conducted with HalfLytely and Bisacodyl Tablets Bowel Prep Kit. It is also not known whether HalfLytely and Bisacodyl Tablets Bowel Prep Kit can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. HalfLytely and Bisacodyl Tablets Bowel Prep Kit should be given to a pregnant or nursing woman only if clearly needed.

Nursing Mothers: It is not known whether HalfLytely and Bisacodyl Tablets Bowel Prep Kit is excreted in human milk, caution should be exercised when HalfLytely and Bisacodyl Tablets Bowel Prep Kit is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients has not been established.

Geriatric Use: There is no evidence for special consideration when administered to elderly patients. Of the total number of subjects in clinical studies (n=186), 28 percent were aged 65 or older, while 9.1 percent were over 75. No overall differences in safety or effectiveness were observed.

ADVERSE REACTIONS

Nausea, cramping and abdominal fullness are the most common adverse reactions (occurring in up to 50% of patients) to administration of HalfLytely and Bisacodyl Tablets Bowel Prep Kit. Vomiting occurs less frequently (approximately 2.7% of patients versus 6.7% of patients taking large volume PEG solutions). In clinical studies, most of these complaints were significantly reduced when compared to the 4 liter preparation. Table 1 shows patient rating of symptoms associated with the preparation from 2 clinical studies (n=400). These adverse reactions are transient and subside rapidly. Isolated cases of urticaria, rhinorrhea, dermatitis and (rarely) anaphylactic reaction have been reported with PEG based products which may represent allergic reactions.

Table 1: Patient Symptom Rating
Bothersome-Severe Complaints

	HalfLytely and Bisacodyl Tablets Bowel Prep Kit	4 liters of PEG electrolyte solution
Nausea	17.1%	31.8%
Cramping	9.1%	17.4%
Fullness	22.3%	44.1%
Vomiting	5.9%	13.7%
Overall Discomfort	19.1%	37.3%

Published literature contains isolated reports of serious adverse reactions following the administration of (4L) PEG-ELS products in patients over 60 years of age. These adverse events include upper GI bleeding from Mallory-Weiss syndrome esophageal perforation, asystole, sudden dyspnea with pulmonary edema, and "butterfly-like" infiltrate on chest X-ray after vomiting and aspirating PEG.

In addition, during administration of 4L PEG-3350 bowel cleansing preparations the following serious adverse events were seen: two deaths in end-stage renal failure patients who developed diarrhea, vomiting, dysnatremia; tonic-clonic seizures in patients with and without prior history of seizures. These adverse events have not been reported in HalfLytely and Bisacodyl Tablets Bowel Prep Kit clinical trials.

DOSAGE AND ADMINISTRATION

HalfLytely and Bisacodyl Tablets Bowel Prep Kit is administered orally. Ideally, the patient should only consume clear liquids (no solid food, no milk) prior to HalfLytely and Bisacodyl Tablets Bowel Prep Kit administration. No antacids should be given for at least one hour before beginning the regimen.

Oral administration: Swallow all four bisacodyl delayed release tablets with water (do **NOT** chew or crush). The first bowel movement should occur in approximately 1-6 hours after taking the bisacodyl delayed release tablets. Wait for a bowel movement (or maximum of 6 hours) then drink the solution at a rate of 1 (8 oz) glass every 10 minutes (approximately 8 glasses). **Drink ALL of the solution.** Rapid drinking of each portion is preferred to drinking small amounts continuously. A watery bowel movement should occur in approximately 1 hour after drinking the solution.

The recommended regimen is to consume clear liquids only (no solid food; no milk) the day of the preparation, take all four bisacodyl delayed release tablets at noon, following the first bowel movement or a maximum of 6 hours, begin drinking the solution.

Preparation of the solution: The solution is prepared by filling the container to the 2 liter mark with water, cap the bottle and shake to dissolve ingredients. Dissolution is facilitated by using lukewarm water. The reconstituted solution may be refrigerated and should be used within 48 hours. All reconstituted solutions are clear and colorless.

HalfLytely and Bisacodyl Tablets Bowel Prep Kit with Flavor Packs contains 3 flavor packs (each 1.0g): Cherry, Lemon-Lime and Orange flavoring, in powdered form, for the addition of ONE pack by the patient. This preparation can be used without the addition of a Flavor Pack.

HOW SUPPLIED

HalfLytely and Bisacodyl Tablets Bowel Prep Kit is available in Lemon-Lime flavor or with Flavor Packs. Each foil lined blister pack contains 4 (5 mg each) bisacodyl delayed release tablets for ingestion prior to drinking of the solution. Each disposable bottle contains powder for oral administration as a solution following reconstitution.

Each HalfLytely and Bisacodyl Tablets Bowel Prep Kit contains:

One pack bisacodyl delayed release tablets: Four (5 mg each) bisacodyl delayed release tablets.

One 2 liter bottle of HalfLytely® (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution): polyethylene glycol 3350 210 g, sodium bicarbonate 2.86 g, sodium chloride 5.60 g, potassium chloride 0.74 g, and 1.0 g flavoring ingredient (if applicable). When made up to 2 liters volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/L.

In addition, each HalfLytely and Bisacodyl Tablets Bowel Prep Kit with Flavor Packs contains 3 packs (each 1.0g) Cherry, Lemon-Lime and Orange Flavors. (optional)

All reconstituted solutions are clear and colorless.

STORAGE: Store at 20-25°C (68-77°F). Excursions permitted between 15-30°C (59-86°F). When reconstituted, you may keep solution refrigerated. Use within 48 hours.

Lemon-Lime HalfLytely and Bisacodyl Tablets Bowel Prep Kit	**NDC 52268-502-01**
HalfLytely and Bisacodyl Tablets Bowel Prep Kit with Flavor Packs	**NDC 52268-520-01**

Distributed by Braintree Laboratories, Inc.
Braintree, MA 02185

Shown in Product Identification Guide, page 308

Bristol-Myers Squibb Company

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ABILIFY® ℞

[ă-bĭl-ĭ-fī]
(aripiprazole) Tablets
ABILIFY®
(aripiprazole) Oral Solution
℞ only

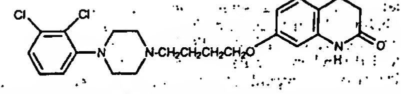
WARNING

Increased Mortality in Elderly Patients With Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis.

DESCRIPTION

ABILIFY® (aripiprazole) is a psychotropic drug that is available as tablets and in solution for oral administration. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dihydrocarbostyril. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The chemical structure is:



ABILIFY tablets are available in 5-mg, 10-mg, 15-mg, 20-mg, and 30-mg strengths. Inactive ingredients include cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

ABILIFY is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution include fructose, glycerin, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose, and purified water. The oral solution is flavored with natural orange cream and other natural flavors.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic and histamine H_1 receptors (K_i values of 44, 15, 39, 57, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K_i=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50} >1000 nM). Aripiprazole functions as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor.

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia and bipolar disorder,

is unknown.
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is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D_2, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole, e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic $alpha_1$ receptors.

Pharmacokinetics

ABILIFY (aripiprazole) activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for D_2 receptors similar to the parent drug and represents 40% of the parent-drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole are dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

Absorption

Tablet: Aripiprazole is well absorbed after administration of the tablet, with peak plasma concentrations occurring within 3 to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. ABILIFY can be administered with or without food. Administration of a 15-mg ABILIFY tablet with a standard high-fat meal did not significantly affect the C_{max} or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed T_{max} by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.

Oral Solution: Aripiprazole is well absorbed when administered orally as the solution. At equivalent doses, the plasma concentrations of aripiprazole from the solution were higher than that from the tablet formulation. In a relative bioavailability study comparing the pharmacokinetics of 30-mg aripiprazole as the oral solution to 30-mg aripiprazole tablets in healthy subjects, the solution to tablet ratios of geometric mean C_{max} and AUC values were 122% and 114%, respectively (see **DOSAGE AND ADMINISTRATION**). The single-dose pharmacokinetics of aripiprazole were linear and dose-proportional between the doses of 5 to 30 mg.

Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent D_2 receptor occupancy indicating brain penetration of aripiprazole in humans.

Metabolism and Elimination

Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. Coadministration of ABILIFY with known inhibitors of CYP2D6, like quinidine in EMs, results in a 112% increase in aripiprazole plasma exposure, and dosing adjustment is needed (see **PRECAUTIONS: Drug-Drug Interactions**). The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in EMs and PMs, respectively. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

Following a single oral dose of [^{14}C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces.

Special Populations

In general, no dosage adjustment for ABILIFY (aripiprazole) is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function (see **DOSAGE AND ADMINISTRATION:** *Dosage in Special Populations*). The pharmacokinetics of aripiprazole in special populations are described below.

Hepatic Impairment

In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

Renal Impairment

In patients with severe renal impairment (creatinine clearance <30 mL/min), C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

Elderly

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients (see **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis,** and **PRECAUTIONS: Geriatric Use**).

Gender

C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

Smoking

Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment is recommended based on smoking status.

Drug-Drug Interactions

Potential for Other Drugs to Affect ABILIFY (aripiprazole)

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (e.g., carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Potential for ABILIFY to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **PRECAUTIONS: Drug-Drug Interactions**).

Aripiprazole had no clinically important interactions with the following drugs:

Famotidine: Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40-mg single dose of the H_2 antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the C_{max} of aripiprazole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

Valproate: When valproate (500–1500 mg/day) and aripiprazole (30 mg/day) were coadministered at steady state, the C_{max} and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when administered concomitantly with valproate.

Lithium: A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200–1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C_{max} and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

Dextromethorphan: Aripiprazole at doses of 10 to 30 mg per day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrorphan, a pathway known to be dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methyoxymorphan, a pathway known to be dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with aripiprazole.

Warfarin: Aripiprazole 10 mg per day for 14 days had no effect on the pharmacokinetics of R- and S-warfarin or on the pharmacodynamic end point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with aripiprazole.

Omeprazole: Aripiprazole 10 mg per day for 15 days had no effect on the pharmacokinetics of a single 20-mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with aripiprazole.

Clinical Studies

Schizophrenia

The efficacy of ABILIFY (aripiprazole) in the treatment of schizophrenia was evaluated in four short-term (4- and 6-week), placebo-controlled trials of acutely relapsed inpatients who predominantly met DSM-III/IV criteria for schizophrenia. Three of the four trials were able to distinguish aripiprazole from placebo, but one study, the smallest, did not. Three of these studies also included an active control group consisting of either risperidone (one trial) or haloperidol (two trials), but they were not designed to allow for a comparison of ABILIFY (aripiprazole) and the active comparators.

In the three positive trials for ABILIFY, four primary measures were used for assessing psychiatric signs and symptoms. The Positive and Negative Syndrome Scale (PANSS) is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. The PANSS positive subscale is a subset of items in the PANSS that rates seven positive symptoms of schizophrenia (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility). The PANSS negative subscale is a subset of items in the PANSS that rates seven negative symptoms of schizophrenia (blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of conversation, stereotyped thinking). The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In a 4-week trial (n=414) comparing two fixed doses of ABILIFY (15 or 30 mg/day) and haloperidol (10 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, and CGI-severity score. In addition, the 15-mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n=404) comparing two fixed doses of ABILIFY (20 or 30 mg/day) and risperidone (6 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n=420) comparing three fixed doses of ABILIFY (10, 15, or 20 mg/day) to placebo, all three doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, and the PANSS negative subscale.

In a fourth study, a 4-week trial (n=103) comparing ABILIFY in a range of 5 to 30 mg/day or haloperidol 5 to 20 mg/day to placebo, haloperidol was superior to placebo, in the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis, and in a responder analysis based on the CGI-severity score, the primary outcomes for that trial. ABILIFY was only significantly different compared to placebo in a responder analysis based on the CGI-severity score.

Thus, the efficacy of 15-mg, 20-mg, and 30-mg daily doses was established in two studies for each dose, whereas the efficacy of the 10-mg dose was established in one study. There was no evidence in any study that the higher dose groups offered any advantage over the lowest dose group. An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were, by history, symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to ABILIFY 15 mg or placebo for up to 26 weeks of observation for relapse. Relapse during the double-blind phase was defined as CGI-Improvement score of ≥5 (minimally worse), scores ≥5 (moderately severe) on the hostility or uncooperativeness items of the PANSS, or ≥20% increase in the PANSS total score. Patients receiving ABILIFY 15 mg experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo.

Bipolar Disorder

The efficacy of ABILIFY in the treatment of acute manic episodes was established in two 3-week, placebo-controlled trials in hospitalized patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes (in one trial, 21% of placebo and 42% of ABILIFY-treated patients had data beyond two weeks). These trials included patients with or without psychotic features and with or without a rapid-cycling course.

Continued on next page

Abilify—Cont.

The primary instrument used for assessing manic symptoms was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). A key secondary instrument included the Clinical Global Impression - Bipolar (CGI-BP) scale.

In the two positive, 3-week, placebo-controlled trials (n=268; n=248) which evaluated ABILIFY (aripiprazole) 15 or 30 mg/day, once daily (with a starting dose of 30 mg/day), ABILIFY was superior to placebo in the reduction of Y-MRS total score and CGI-BP Severity of Illness score (mania).

A trial was conducted in patients meeting DSM-IV criteria for Bipolar I Disorder with a recent manic or mixed episode who had been stabilized on open-label ABILIFY and who had maintained a clinical response for at least 6 weeks. The first phase of this trial was an open-label stabilization period in which inpatients and outpatients were clinically stabilized and then maintained on open-label ABILIFY (15 or 30 mg/day, with a starting dose of 30 mg/day) for at least 6 consecutive weeks. One hundred sixty-one outpatients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization and maintenance period or placebo and were then monitored for manic or depressive relapse. During the randomization phase, ABILIFY was superior to placebo on time to the number of combined affective relapses (manic plus depressive), the primary outcome measure for this study. The majority of these relapses were due to manic rather than depressive symptoms. There is insufficient data to know whether ABILIFY is effective in delaying the time to occurrence of depression in patients with Bipolar I Disorder.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age and gender; however, there were insufficient numbers of patients in each of the ethnic groups to adequately assess inter-group differences.

INDICATIONS AND USAGE

Schizophrenia

ABILIFY is indicated for the treatment of schizophrenia.

The efficacy of ABILIFY in the treatment of schizophrenia was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

The efficacy of ABILIFY in maintaining stability in patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those other medications, and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks was demonstrated in a placebo-controlled trial (see **CLINICAL PHARMACOLOGY: Clinical Studies**). The physician who elects to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Bipolar Disorder

ABILIFY is indicated for the treatment of acute manic and mixed episodes associated with Bipolar Disorder.

The efficacy of ABILIFY was established in two placebo-controlled trials (3-week) of inpatients with DSM-IV criteria for Bipolar I Disorder who were experiencing an acute manic or mixed episode with or without psychotic features (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

The efficacy of ABILIFY in maintaining efficacy in patients with Bipolar I Disorder with a recent manic or mixed episode who had been stabilized and then maintained for at least 6 weeks, was demonstrated in a double-blind, placebo-controlled trial. Prior to entering the double-blind, randomization phase of this trial, patients were clinically stabilized and maintained their stability for 6 consecutive weeks on ABILIFY (aripiprazole). Following this 6-week maintenance phase, patients were randomized to either placebo or ABILIFY and monitored for relapse (see **CLINICAL PHARMACOLOGY: Clinical Studies**). Physicians who elect to use ABILIFY for extended periods, that is, longer than 6 weeks, should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

ABILIFY is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Increased Mortality in Elderly Patients With Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ABILIFY is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including aripiprazole. Two possible cases of NMS occurred during aripiprazole treatment in the premarketing worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY (aripiprazole) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled clinical studies (two flexible-dose and one fixed-dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78–88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis. (See also Boxed WARNING; **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**, and **PRECAUTIONS**: *Use in Patients with Concomitant Illness: Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease*.)

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with ABILIFY. Although fewer patients have been treated with ABILIFY, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include ABILIFY (aripiprazole) suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on ABILIFY (aripiprazole) included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials in bipolar mania (n=597) on ABILIFY included: orthostatic hypotension (placebo 0%, aripiprazole 0.7%), orthostatic lightheadedness (placebo 0.5%, aripiprazole 0.5%), and syncope (placebo 0.9%, aripiprazole 0.5%).

The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not statistically different from placebo (in schizophrenia: 14% among aripiprazole-treated patients and 12% among placebo-treated patients and in bipolar mania: 3% among aripiprazole-treated patients and 2% among placebo-treated patients).

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizure

Seizures occurred in 0.1% (1/926) of aripiprazole-treated patients with schizophrenia in short-term, placebo-controlled trials. In short-term, placebo-controlled clinical trials of patients with bipolar mania, 0.3% (2/597) of aripiprazole-treated patients and 0.2% (1/436) of placebo-treated patients experienced seizures. As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment

In short-term, placebo-controlled trials of schizophrenia, somnolence was reported in 11% of patients on ABILIFY compared to 8% of patients on placebo; somnolence led to discontinuation in 0.1% (1/926) of patients with schizophrenia on ABILIFY in short-term, placebo-controlled trials. In short-term, placebo-controlled trials of bipolar mania, somnolence was reported in 14% of patients on ABILIFY compared to 7% of patients on placebo, but did not lead to discontinuation of any patients with bipolar mania. Despite the relatively modest increased incidence of somnolence compared to placebo, ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's de-

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mentia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **PRECAUTIONS:** *Use in Patients with Concomitant Illness*).

Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY (aripiprazole) should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness

Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses (see **CLINICAL PHARMACOLOGY: Special Populations:** *Renal Impairment* and *Hepatic Impairment*) is limited.

ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies.

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease: In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56–99 years), the treatment-emergent adverse events that were reported at an incidence of ≥5% and aripiprazole incidence at least twice that for placebo were asthenia (placebo 3%, aripiprazole 8%), somnolence (placebo 3%, aripiprazole 9%), and urinary incontinence (placebo 1%, aripiprazole 5%).

The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration. (See also **Boxed WARNING** and **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis** and **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis.**)

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY:

Interference with Cognitive and Motor Performance

Because aripiprazole may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that aripiprazole therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY.

Nursing

Patients should be advised not to breast-feed an infant if they are taking ABILIFY.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking ABILIFY.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Sugar Content

Patients should be advised that each mL of ABILIFY (aripiprazole) oral solution contains 400 mg of sucrose and 200 mg of fructose.

Drug-Drug Interactions

Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally acting drugs and alcohol. Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Potential for Other Drugs to Affect ABILIFY

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (e.g., carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Ketoconazole: Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; weaker inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Quinidine: Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when concomitant administration of quinidine with aripiprazole occurs. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and, therefore, should be accompanied by similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Carbamazepine: Coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg QD) resulted in an approximate 70% decrease in C_{max} and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, aripiprazole dose should then be reduced.

No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**).

Potential for ABILIFY (aripiprazole) to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**).

Alcohol: There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in CHL cells with and without metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the *in vitro* assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the *in vivo* micronucleus assay in mice, however, the response was shown to be due to a mechanism not considered relevant to humans.

Impairment of Fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg, and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m^2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

Pregnancy

Pregnancy Category C

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg, however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of skeletal abnormality (fused sternebrae at 30 and 100 mg/kg) and minor skeletal variations (100 mg/kg).

In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and decreases in pup weight (persisting into adulthood) and survival, were seen at this dose.

There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Labor and Delivery

The effect of aripiprazole on labor and delivery in humans is unknown.

Nursing Mothers

Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.

Pediatric Use

Safety and effectiveness in pediatric and adolescent patients have not been established.

Geriatric Use

Of the 7951 patients treated with aripiprazole in premarketing clinical trials, 991 (12%) were ≥65 years old and 789 (10%) were ≥75 years old. The majority (88%) of the 991 patients were diagnosed with dementia of the Alzheimer's type.

Placebo-controlled studies of aripiprazole in schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There was no effect of age on the pharmacokinetics of a single 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects (≥65 years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia (see **Boxed WARNING** and **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis and Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis** and **PRECAUTIONS:** *Use in Patients with Concomitant Illness*). The safety and efficacy of ABILIFY (aripiprazole) in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 7951 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 5235 patient-years of exposure. A total of 2280 aripiprazole-treated patients were treated for at least 180 days and 1558 aripiprazole-treated patients had at least 1 year of exposure.

Continued on next page

Abilify—Cont.

The conditions and duration of treatment with aripiprazole included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure.

Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; i.e., all reported events are included.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Schizophrenia

The following findings are based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which aripiprazole was administered in doses ranging from 2 to 30 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole- and placebo-treated patients.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

The following findings are based on a pool of 3-week, placebo-controlled, bipolar mania trials in which aripiprazole was administered at doses of 15 or 30 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, in patients with bipolar mania, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (11%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

Commonly observed adverse events associated with the use of aripiprazole in patients with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 1. There were no adverse events in the short-term trials of schizophrenia that met these criteria.

Table 1: Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

Adverse Event	Percentage of Patients Reporting Event Aripiprazole (n=597)	Placebo (n=436)
Accidental Injury	6	3
Constipation	13	6
Akathisia	15	4

Adverse Events Occurring at an Incidence of 2% or More Among Aripiprazole-Treated Patients and Greater than Placebo in Short-Term, Placebo-Controlled Trials

Table 2 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those events that occurred in 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 2: Treatment-Emergent Adverse Events In Short-Term, Placebo-Controlled Trials

Body System Adverse Event	Percentage of Patients Reporting Event[a] Aripiprazole (n=1523)	Placebo (n=849)
Body as a Whole		
Headache	31	26
Asthenia	8	7
Accidental Injury	5	4
Peripheral Edema	2	1
Cardiovascular System		
Hypertension	2	1
Digestive System		
Nausea	16	12
Dyspepsia	15	13
Vomiting	11	6
Constipation	11	7
Musculoskeletal System		
Myalgia	4	3
Nervous System		
Agitation	25	24
Anxiety	20	17
Insomnia	20	15
Somnolence	12	8
Akathisia	12	5
Lightheadedness	11	8
Extrapyramidal Syndrome	6	4
Tremor	4	3
Increased Salivation	3	1
Respiratory System		
Pharyngitis	4	3
Rhinitis	4	3
Coughing	3	2
Special Senses		
Blurred vision	3	1

[a] Events reported by at least 2% of patients treated with aripiprazole, except the following events, which had an incidence equal to or less than placebo: abdominal pain, back pain, dental pain, diarrhea, dry mouth, anorexia, psychosis, hypertonia, upper respiratory tract infection, rash, vaginitis[f], dysmenorrhea[f].

[f] Percentage based on gender total.

An examination of population subgroups did not reveal any clear evidence of differential adverse event incidence on the basis of age, gender, or race.

Dose-Related Adverse Events

Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in patients with schizophrenia comparing various fixed doses (2, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

Extrapyramidal Symptoms

In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 17% vs. 12% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of akathisia-related events for aripiprazole-treated patients was 15% vs. 4% for placebo. Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, −0.05). In the bipolar mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25; placebo, −0.06). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

Table 3: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample

	BMI <23		BMI 23–27		BMI >27	
	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole
Mean change from baseline (kg)	−0.5	−0.5	−0.6	−1.3	−1.5	−2.1
% with ≥7% increase BW	3.7%	6.8%	4.2%	5.1%	4.1%	5.7%

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

Laboratory Test Abnormalities

A between group comparison for 3- to 6-week, placebo-controlled trials revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis.

In a long-term (26-week), placebo-controlled trial there were no medically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, and total cholesterol measurements.

Weight Gain

In 4- to 6-week trials in schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. −0.05 kg, respectively), and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (8%) compared to placebo (3%)]. In 3-week trials in mania, the mean weight gain for aripiprazole and placebo patients was 0.0 kg vs. −0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (3%) compared to placebo (2%).

Table 3 provides the weight change results from a long-term (26-week), placebo-controlled study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

[See table 3 below]

Table 4 provides the weight change results from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 4: Weight Change Results Categorized by BMI at Baseline: Active-Controlled Study in Schizophrenia, Safety Sample.

	BMI <23	BMI 23−27	BMI >27
Mean change from baseline (kg)	2.6	1.4	−1.2
% with ≥7% increase BW	30%	19%	8%

ECG Changes

Between group comparisons for a pooled analysis of placebo-controlled trials in patients with schizophrenia or bipolar mania, revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. Aripiprazole was associated with a median increase in heart rate of 5 beats per minute compared to a 1 beat per minute increase among placebo patients.

Additional Findings Observed in Clinical Trials

Adverse Events in Long-Term, Double-Blind, Placebo-Controlled Trials

The adverse events reported in a 26-week, double-blind trial comparing ABILIFY (aripiprazole) and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [9% (13/153) for ABILIFY vs. 1% (2/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13 ≤49 days), and were of limited duration (9/13 ≤10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor for ABILIFY was 4% (34/859). A similar adverse event profile was observed in a long-term study in bipolar disorder.

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 7951 patients. All reported events are included except those already listed in Table 2, or other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to be uninformative, events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in

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at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent – flu syndrome, fever, chest pain, rigidity (including neck and extremity), neck pain, pelvic pain; *Infrequent* – face edema, suicide attempt, malaise, migraine, chills, photosensitivity, tightness (including abdomen, back, extremity, head, jaw, neck, and tongue), jaw pain, bloating, enlarged abdomen, chest tightness, throat pain; *Rare* – moniliasis, head heaviness, throat tightness, Mendelson's syndrome, heat stroke.

Cardiovascular System: Frequent – tachycardia (including ventricular and supraventricular), hypotension, bradycardia; *Infrequent* – palpitation, hemorrhage, heart failure, myocardial infarction, cardiac arrest, atrial fibrillation, AV block, prolonged QT interval, extrasystoles, myocardial ischemia, deep vein thrombosis, angina pectoris, pallor, cardiopulmonary arrest, phlebitis; *Rare* – bundle branch block, atrial flutter, vasovagal reaction, cardiomegaly, thrombophlebitis, cardiopulmonary failure.

Digestive System: Frequent – nausea and vomiting; *Infrequent* – increased appetite, dysphagia, gastroenteritis, flatulence, tooth caries, gastritis, gingivitis, gastrointestinal hemorrhage, hemorrhoids, gastroesophageal reflux, periodontal abscess, fecal incontinence, rectal hemorrhage, stomatitis, colitis, tongue edema, cholecystitis, mouth ulcer, oral moniliasis, eructation, fecal impaction, cholelithiasis; *Rare* – esophagitis, hematemesis, intestinal obstruction, gum hemorrhage, hepatitis, peptic ulcer, glossitis, melena, duodenal ulcer, cheilitis, hepatomegaly, pancreatitis.

Endocrine System: Infrequent – hypothyroidism; *Rare* – goiter, hyperthyroidism.

Hemic/Lymphatic System: Frequent – ecchymosis, anemia; *Infrequent* – hypochromic anemia, leukocytosis, leukopenia (including neutropenia), lymphadenopathy, eosinophilia, macrocytic anemia; *Rare* – thrombocythemia, thrombocytopenia, petechiae.

Metabolic and Nutritional Disorders: Frequent – weight loss, creatine phosphokinase increased, dehydration; *Infrequent* – edema, hyperglycemia, hypercholesteremia, hypokalemia, diabetes mellitus, hypoglycemia, hyperlipemia, SGPT increased, thirst, BUN increased, hyponatremia, SGOT increased, creatinine increased, cyanosis, alkaline phosphatase increased, bilirubinemia, iron deficiency anemia, hyperkalemia, hyperuricemia, obesity; *Rare* – lactic dehydrogenase increased, hypernatremia, gout, hypoglycemic reaction.

Musculoskeletal System: Frequent – muscle cramp; *Infrequent* – arthralgia, myasthenia, arthrosis, bone pain, arthritis, muscle weakness, spasm, bursitis, myopathy; *Rare* – rheumatoid arthritis, rhabdomyolysis, tendonitis, tenosynovitis.

Nervous System: Frequent – depression, nervousness, schizophrenic reaction, hallucination, hostility, confusion, paranoid reaction, suicidal thought, abnormal gait, manic reaction, delusions, abnormal dream; *Infrequent* – emotional lability, twitch, cogwheel rigidity, impaired concentration, dystonia, vasodilation, paresthesia, impotence, extremity tremor, hypesthesia, vertigo, stupor, bradykinesia, apathy, panic attack, decreased libido, hypersomnia, dyskinesia, manic depressive reaction, ataxia, visual hallucination, cerebrovascular accident, hypokinesia, depersonalization, impaired memory, delirium, dysarthria, tardive dyskinesia, amnesia, hyperactivity, increased libido, myoclonus, restless leg, neuropathy, dysphoria, hyperkinesia, cerebral ischemia, increased reflexes, akinesia, decreased consciousness, hyperesthesia, slowed thinking; *Rare* – blunted affect, euphoria, incoordination, oculogyric crisis, obsessive thought; hypotonia, buccoglossal syndrome, decreased reflexes, derealization, intracranial hemorrhage.

Respiratory System: Frequent – sinusitis, dyspnea, pneumonia, asthma; *Infrequent* – epistaxis, hiccup, laryngitis, aspiration pneumonia; *Rare* – pulmonary edema, increased sputum, pulmonary embolism, hypoxia, respiratory failure, apnea, dry nasal passages, hemoptysis.

Skin and Appendages: Frequent – skin ulcer, sweating, dry skin; *Infrequent* – pruritus, vesiculobullous rash, acne, eczema, skin discoloration, alopecia, seborrhea, psoriasis; *Rare* – maculopapular rash, exfoliative dermatitis, urticaria.

Special Senses: Frequent – conjunctivitis; *Infrequent* – ear pain, dry eye, eye pain, tinnitus, cataract, otitis media, altered taste, blepharitis, eye hemorrhage, deafness; *Rare* – diplopia, frequent blinking, ptosis, otitis externa, amblyopia, photophobia.

Urogenital System: Frequent – urinary incontinence; *Infrequent* – urinary frequency, leukorrhea, urinary retention, cystitis, hematuria, dysuria, amenorrhea, vaginal hemorrhage, abnormal ejaculation, kidney failure, vaginal moniliasis, urinary urgency, gynecomastia, kidney calculus, albuminuria, breast pain, urinary burning; *Rare* – nocturia, polyuria, menorrhagia, anorgasmy, glycosuria, cervicitis, uterus hemorrhage, female lactation, urolithiasis, priapism.

Other Events Observed During the Postmarketing Evaluation of Aripiprazole

Voluntary reports of adverse events in patients taking aripiprazole that have been received since market introduction and not listed above that may have no causal relationship with the drug include rare occurrences of allergic reaction (e.g., anaphylactic reaction, angioedema, laryngospasm, pruritis, or urticaria).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

ABILIFY (aripiprazole) is not a controlled substance.

Abuse and Dependence

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

In clinical studies, accidental or intentional acute overdosage of aripiprazole was identifed in patients with estimated doses up to 1080 mg with no fatalities. The reported signs and symptoms observed with aripiprazole overdose included nausea, vomiting, asthenia, diarrhea, and somnolence. In the patients who were evaluated in hospital settings, there were no reported observations indicating clinically significant adverse change in vital signs, laboratory assessments, or ECG.

During postmarketing experience, the reported signs and symptoms observed in adult patients who overdosed with aripiprazole alone at doses up to 450 mg included tachycardia. In addition, reports of accidental overdose with aripiprazole (up to 195 mg) in children have been received. The potentially medically serious signs and symptoms reported include extrapyramidal symptoms and transient loss of consciousness with recovery.

Management of Overdosage

No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and, if QTc interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal: In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of aripiprazole by 50%.

Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Dose

The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day, when administered as the tablet formulation, however, doses higher than 10 or 15 mg/day, the lowest doses in these trials, were not more effective than 10 or 15 mg/day. Dosage increases should not be made before 2 weeks, the time needed to achieve steady state.

Dosage in Special Populations

Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment status (see **CLINICAL PHARMACOLOGY: Special Populations**).

Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP3A4 inhibitors: When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of the usual dose. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP2D6 inhibitors: When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, aripiprazole dose should be reduced at least to one-half of its normal dose. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Dosage adjustment for patients taking potential CYP3A4 inducers: When a potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be doubled (to 20 or 30 mg). Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced to 10 to 15 mg.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, systematic evaluation of patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those medications, and were then administered ABILIFY (aripiprazole) 15 mg/day and observed for relapse during a period of up to 26 weeks, demonstrated a benefit of such maintenance treatment (see **CLINICAL PHARMACOLOGY: Clinical Studies**). Patients should be periodically reassessed to determine the need for maintenance treatment.

Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

Bipolar Disorder

Usual Dose

In clinical trials, the starting dose was 30 mg given once a day. A dose of 30 mg/day was found to be effective when administered as the tablet formulation. Approximately 15% of patients had their dose decreased to 15 mg based on assessment of tolerability. The safety of doses above 30 mg/day has not been evaluated in clinical trials.

Dosage in Special Populations

See *Dosage in Special Populations* under **DOSAGE AND ADMINISTRATION: Schizophrenia.**

Maintenance Therapy

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, patients with Bipolar I Disorder who had been symptomatically stable on ABILIFY Tablets (15 mg/day or 30 mg/day with a starting dose of 30 mg/day) for at least 6 consecutive weeks and then randomized to ABILIFY Tablets (15 mg/day or 30 mg/day) or placebo and monitored for relapse, demonstrated a benefit of such maintenance treatment (see **CLINICAL PHARMACOLOGY: Clinical Studies**). While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of aripiprazole in such longer-term treatment (i.e., beyond 6 weeks).

Oral Solution

The oral solution can be given on a mg-per-mg basis in place of the 5-, 10-, 15-, or 20-mg tablet strengths. Solution doses can be substituted for the tablet doses on a mg-per-mg basis up to 25 mg of the tablet. Patients receiving 30-mg tablets should receive 25 mg of the solution (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

ANIMAL TOXICOLOGY

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40- and 60-mg/kg doses are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m^2 and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

HOW SUPPLIED

ABILIFY® (aripiprazole) Tablets are available in the following strengths and packages.

The 5-mg ABILIFY tablets are blue, modified rectangular tablets, debossed on one side with "A-007" and "5".

Bottles of 30	NDC 59148-007-13
Blister of 100	NDC 59148-007-35

The 10-mg ABILIFY tablets are pink, modified rectangular tablets, debossed on one side with "A-008" and "10".

Bottles of 30	NDC 59148-008-13
Blister of 100	NDC 59148-008-35

The 15-mg ABILIFY tablets are yellow, round tablets, debossed on one side with "A-009" and "15".

Bottles of 30	NDC 59148-009-13
Blister of 100	NDC 59148-009-35

The 20-mg ABILIFY tablets are white, round tablets, debossed on one side with "A-010" and "20".

Bottles of 30	NDC 59148-010-13
Blister of 100	NDC 59148-010-35

The 30-mg ABILIFY tablets are pink, round tablets, debossed on one side with "A-011" and "30".

Bottles of 30	NDC 59148-011-13
Blister of 100	NDC 59148-011-35

ABILIFY® (aripiprazole) Oral Solution (1 mg/mL) is supplied in child-resistant bottles along with a calibrated oral dosing cup. ABILIFY oral solution is available as follows:

150-mL bottle	NDC 59148-012-15

Storage

Tablets

Store at 25° C (77° F); excursions permitted to 15° C to 30° C (59° F to 86° F) [see USP Controlled Room Temperature].

Oral Solution

Store in a refrigerator at 2° C to 8° C (36° F to 46° F). Open bottles of ABILIFY oral solution should be stored in a refrigerator and can be used for up to 6 months after opening.

Continued on next page

Abilify—Cont.

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd.; Tokyo, 101-8535 Japan or Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
Oral Solution manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA
Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
U.S. Patent Nos. 4,734,416 and 5,006,528
Bristol-Myers Squibb Company
Princeton, NJ 08543 U.S.A.
Otsuka America Pharmaceutical, Inc.
Rockville, MD 20850 U.S.A.
AP4996/04-05 1156731B4
D6-B0001-04-05 Revised April 2005

Shown in Product Identification Guide, page 309

AVALIDE® ℞

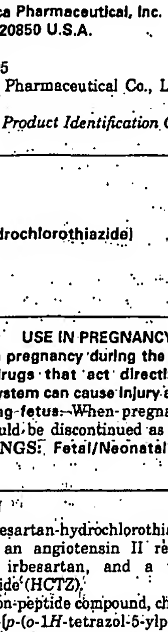
[*avă·līde*]
(irbesartan-hydrochlorothiazide)
Tablets
Rx only

> **USE IN PREGNANCY**
> **When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.** When pregnancy is detected, AVALIDE should be discontinued as soon as possible. (See WARNINGS: **Fetal/Neonatal Morbidity and Mortality.**)

DESCRIPTION

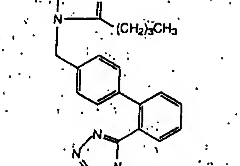
AVALIDE®* (irbesartan-hydrochlorothiazide) Tablets is a combination of an angiotensin II receptor antagonist (AT_1 subtype), irbesartan, and a thiazide diuretic, hydrochlorothiazide (HCTZ).

Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro [4.4]non-1-en-4-one. Its empirical formula is $C_{25}H_{28}N_6O$, and its structural formula is:



Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.5. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzo-thiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.7. Hydrochlorothiazide is slightly soluble in water and freely soluble in sodium hydroxide solution.

AVALIDE is available for oral administration in tablets containing either 150 mg or 300 mg of irbesartan combined with 12.5 mg of hydrochlorothiazide or 300 mg of irbesartan combined with 25 mg hydrochlorothiazide. Inactive ingredients include: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, ferric oxide red, ferric oxide yellow, silicon dioxide, and magnesium stearate. In addition, the 300/25 mg pink film-coated tablet contains ferric oxide black, hypromellose-2910, PEG-3350, titanium dioxide, and carnauba wax.

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*Registered trademark of Sanofi-Synthelabo

CLINICAL PHARMACOLOGY

Mechanism of Action

Irbesartan

Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT_1 angiotensin II receptor. There is also an AT_2 receptor in many tissues, but it is not involved in cardiovascular homeostasis.

Irbesartan is a specific competitive antagonist of AT_1 receptors with a much greater affinity (more than 8500-fold) for the AT_1 receptor than for the AT_2 receptor and no agonist activity.

Blockade of the AT_1 receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effects of irbesartan on blood pressure.

Irbesartan does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in the cardiovascular regulation of blood pressure and sodium homeostasis. Because irbesartan does not inhibit ACE, it does not affect the response to bradykinin; whether this has clinical relevance is not known.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is not fully understood.

Pharmacokinetics

Irbesartan

Irbesartan is an orally active agent that does not require biotransformation into an active form. The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60–80%. Following oral administration of irbesartan, peak plasma concentrations of irbesartan are attained at 1.5–2 hours after dosing. Food does not affect the bioavailability of irbesartan.

Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range.

The terminal elimination half-life of irbesartan averaged 11–15 hours. Steady-state concentrations are achieved within 3 days. Limited accumulation of irbesartan (<20%) is observed in plasma upon repeated once-daily dosing.

Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Metabolism and Elimination

Irbesartan

Irbesartan is metabolized via glucuronide conjugation and oxidation. Following oral or intravenous administration of ^{14}C-labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributable to unchanged irbesartan. The primary circulating metabolite is the inactive irbesartan glucuronide conjugate (approximately 6%). The remaining oxidative metabolites do not add appreciably to irbesartan's pharmacologic activity.

Irbesartan and its metabolites are excreted by both biliary and renal routes. Following either oral or intravenous administration of ^{14}C-labeled irbesartan, about 20% of radioactivity is recovered in the urine and the remainder in the feces, as irbesartan or irbesartan glucuronide.

In vitro studies of irbesartan oxidation by cytochrome P450 isoenzymes indicated irbesartan was oxidized primarily by 2C9; metabolism by 3A4 was negligible. Irbesartan was neither metabolized by, nor did it substantially induce or inhibit, isoenzymes commonly associated with drug metabolism (1A1, 1A2, 2A6, 2B6, 2D6, 2E1). There was no induction or inhibition of 3A4.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

Distribution

Irbesartan

Irbesartan is 90% bound to serum proteins (primarily albumin and α_1-acid glycoprotein) with negligible binding to cellular components of blood. The average volume of distribution is 53–93 liters. Total plasma and renal clearances are in the range of 157–176 and 3.0–3.5 mL/min, respectively. With repetitive dosing, irbesartan accumulates to no clinically relevant extent.

Studies in animals indicate that radiolabeled irbesartan weakly crosses the blood-brain barrier and placenta. Irbesartan is excreted in the milk of lactating rats.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Special Populations

Pediatric

Irbesartan pharmacokinetics have not been investigated in patients <18 years of age.

Gender

No gender-related differences in pharmacokinetics were observed in healthy elderly (age 65–80 years) or in healthy young (age 18–40 years) subjects. In studies of hypertensive patients, there was no gender difference in half-life or accumulation, but somewhat higher plasma concentrations of irbesartan were observed in females (11–44%). No gender-related dosage adjustment is necessary.

Geriatric

In elderly subjects (age 65–80 years), irbesartan elimination half-life was not significantly altered, but AUC and C_{max} values were about 20–50% greater than those of young subjects (age 18–40 years). No dosage adjustment is necessary in the elderly.

Race

In healthy black subjects, irbesartan AUC values were approximately 25% greater than whites; there were no differences in C_{max} values.

Renal Insufficiency

The pharmacokinetics of irbesartan were not altered in patients with renal impairment or in patients on hemodialysis. Irbesartan is not removed by hemodialysis. No dosage adjustment is necessary in patients with mild to severe renal impairment unless a patient with renal impairment is also volume depleted. (See WARNINGS: **Hypotension in Volume- or Salt-depleted Patients** and DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

The pharmacokinetics of irbesartan following repeated oral administration were not significantly affected in patients with mild to moderate cirrhosis of the liver. No dosage adjustment is necessary in patients with hepatic insufficiency.

Drug Interactions

(See PRECAUTIONS: **Drug Interactions.**)

Pharmacodynamics

Irbesartan

In healthy subjects, single oral irbesartan doses of up to 300 mg produced dose-dependent inhibition of the pressor effect of angiotensin II infusions. Inhibition was complete (100%) 4 hours following oral doses of 150 mg or 300 mg and partial inhibition was sustained for 24 hours (60% and 40% at 300 mg and 150 mg, respectively).

In hypertensive patients, angiotensin II receptor inhibition following chronic administration of irbesartan causes a 1.5–2 fold rise in angiotensin II plasma concentration and a 2–3 fold increase in plasma renin levels. Aldosterone plasma concentrations generally decline following irbesartan administration, but serum potassium levels are not significantly affected at recommended doses.

In hypertensive patients, chronic oral doses of irbesartan (up to 300 mg) had no effect on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no clinically important effects on fasting triglycerides, total cholesterol, HDL-cholesterol, or fasting glucose concentrations. There was no effect on serum uric acid during chronic oral administration and no uricosuric effect.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Clinical Studies

Irbesartan

The antihypertensive effects of irbesartan were examined in seven (7) major placebo-controlled 8–12 week trials in patients with baseline diastolic blood pressures of 95–110 mmHg. Doses of 1–900 mg were included in these trials in order to fully explore the dose-range of irbesartan. These studies allowed a comparison of once- or twice-daily regimens at 150 mg/day, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Two of the seven placebo-controlled trials identified above and two additional placebo-controlled studies examined the antihypertensive effects of irbesartan and hydrochlorothiazide in combination.

The seven (7) studies of irbesartan monotherapy included a total of 1915 patients randomized to irbesartan (1–900 mg) and 611 patients randomized to placebo. Once-daily doses of 150 to 300 mg provided statistically and clinically significant decreases in systolic and diastolic blood pressure with trough (24 hour post-dose) effects after 6–12 weeks of treatment compared to placebo, of about 8–10/5–6 and 8–12/5–8 mmHg, respectively. No further increase in effect was seen at dosages greater than 300 mg. The dose-response relationships for effects on systolic and diastolic pressure are shown in Figures 1 and 2.

[See figure 1 at top of next column]

[See figure 2 at top of next column]

Once-daily administration of therapeutic doses of irbesartan gave peak effects at around 3–6 hours and, in one continuous ambulatory blood pressure monitoring study, and again around 14 hours. This was seen with both once-daily and twice-daily dosing. Trough-to-peak ratios for systolic and diastolic response were generally between 60–70%.

In a continuous ambulatory blood pressure monitoring study, once-daily dosing with 150 mg gave trough and mean 24-hour responses similar to those observed in patients receiving twice-daily dosing at the same total daily dose.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65 years of age, had generally similar responses. Irbesartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in blacks (usually a low-renin population). Black patients typically show an improved response with the addition of a low dose diuretic (e.g., 12.5 mg hydrochlorothiazide).

STRATTERA® Capsules	10 mg*	18 mg*	25 mg*	40 mg*	60 mg*
Color	Opaque White, Opaque White	Gold, Opaque White	Opaque Blue, Opaque White	Opaque Blue, Opaque Blue	Opaque Blue, Gold.
Identification	LILLY 3227 10 mg	LILLY 3238 18 mg	LILLY 3228 25 mg	LILLY 3229 40 mg	LILLY 3239 60 mg
NDC Codes:					
Bottles of 30	0002-3227-30	0002-3238-30	0002-3228-30	0002-3229-30	0002-3239-30
Bottles of 2000	0002-3227-07	0002-3238-07	0002-3228-07	0002-3229-07	0002-3239-07

*Atomoxetine base equivalent.

Strattera—Cont.

dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day (*see* CLINICAL STUDIES).

The total daily dose in children and adolescents should not exceed 1.4 mg/kg or 100 mg, whichever is less.

Dosing of children and adolescents over 70 kg body weight and adults—STRATTERA should be initiated at a total daily dose of 40 mg and increased after a minimum of 3 days to a target total daily dose of approximately 80 mg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. After 2 to 4 additional weeks, the dose may be increased to a maximum of 100 mg in patients who have not achieved an optimal response. There are no data that support increased effectiveness at higher doses (*see* CLINICAL STUDIES).

The maximum recommended total daily dose in children and adolescents over 70 kg and adults is 100 mg.

Maintenance/Extended Treatment

There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with STRATTERA. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use STRATTERA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

General Dosing Information

STRATTERA may be taken with or without food.

The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated.

Dosing adjustment for hepatically impaired patients—For those ADHD patients who have hepatic insufficiency (HI), dosage adjustment is recommended as follows: For patients with moderate HI (Child-Pugh Class B), initial and target doses should be reduced to 50% of the normal dose (for patients without HI). For patients with severe HI (Child-Pugh Class C), initial dose and target doses should be reduced to 25% of normal (*see* Special Populations *under* CLINICAL PHARMACOLOGY).

Dosing adjustment for use with a strong CYP2D6 inhibitor—In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

Atomoxetine can be discontinued without being tapered.

HOW SUPPLIED

STRATTERA® (atomoxetine HCl) capsules are supplied in 10-, 18-, 25-, 40-, and 60-mg strengths.

[See table above]

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Literature revised April 6, 2005

PV 3757 AMP

Shown in Product Identification Guide, page 320

SYMBYAX® ℞

[sim·bee-ax]

(olanzapine and fluoxetine HCl capsules)

WARNING

Suicidality in Children and Adolescents—Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients. (*See* WARNINGS *and* PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infections (e.g., pneumonia) in nature. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis (*see* WARNINGS).

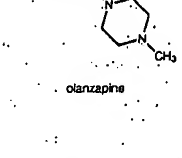
DESCRIPTION

SYMBYAX® (olanzapine and fluoxetine HCl capsules) combines 2 psychotropic agents; olanzapine (the active ingredient in Zyprexa®, and Zyprexa Zydis®) and fluoxetine hydrochloride (the active ingredient in Prozac®, Prozac Weekly™, and Sarafem®).

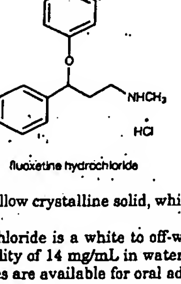
Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44.

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The chemical designation is (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride. The molecular formula is $C_{17}H_{18}F_3NO \cdot HCl$, which corresponds to a molecular weight of 345.79.

The chemical structures are:



olanzapine



fluoxetine hydrochloride

Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

SYMBYAX capsules are available for oral administration in the following strength combinations:

	6 mg/ 25 mg	6 mg/ 50 mg	12 mg/ 25 mg	12 mg/ 50 mg
olanzapine equivalent	6	6	12	12
fluoxetine base equivalent	25	50	25	50

Each capsule also contains pregelatinized starch, gelatin, dimethicone; titanium dioxide, sodium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, and/or black iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Although the exact mechanism of SYMBYAX is unknown, it has been proposed that the activation of 3 monoaminergic neural systems (serotonin, norepinephrine, and dopamine) is responsible for its enhanced antidepressant effect. This is supported by animal studies in which the olanzapine/fluoxetine combination has been shown to produce synergistic increases in norepinephrine and dopamine release in the prefrontal cortex compared with either component alone, as well as increases in serotonin.

Olanzapine is a psychotropic agent with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ (K_i=4 and 11 nM, respectively), dopamine D_{1-4} (K_i=11 to 31 nM), muscarinic M_{1-5} (K_i=1.9 to 25 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors, (K_i=19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors (K_i>10 μM). Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic effects. The antagonism of histamine H_1 receptors by olanzapine may explain the somnolence observed with this drug. The antagonism of α_1-adrenergic receptors by olanzapine may explain the orthostatic hypotension observed with this drug. Fluoxetine has relatively low affinity for muscarinic, α_1-adrenergic, and histamine H_1 receptors.

Pharmacokinetics

Fluoxetine (administered as a 60-mg single dose or 60 mg daily for 8 days) caused a small increase in the mean maximum concentration of olanzapine (16%) following a 5-mg dose, an increase in the mean area under the curve (17%) and a small decrease in mean apparent clearance of olanzapine (16%). In another study, a similar decrease in apparent clearance of olanzapine of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more. The decrease in clearance reflects an increase in bioavailability. The terminal half-life is not affected, and therefore the time to reach steady state should not be altered. The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies. The small change in olanzapine clearance, observed in both studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination.

Absorption and Bioavailability

SYMBYAX—Following a single oral 12-mg/50-mg dose of SYMBYAX, peak plasma concentrations of olanzapine and fluoxetine occur at approximately 4 and 6 hours, respectively. The effect of food on the absorption and bioavailability of SYMBYAX has not been evaluated. The bioavailability of olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as Prozac were not affected by food. It is unlikely that there would be a significant food effect on the bioavailability of SYMBYAX.

Olanzapine—Olanzapine is well absorbed and reaches peak concentration approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption when olanzapine is given as Zyprexa. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.

Fluoxetine—Following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine given as Prozac, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.

Distribution

SYMBYAX—The in vitro binding to human plasma proteins of the olanzapine/fluoxetine combination is similar to the binding of the individual components.

Olanzapine—Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1-acid glycoprotein.

Fluoxetine—Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and

glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated (*see* PRECAUTIONS, Drugs tightly bound to plasma proteins).

Metabolism and Elimination

SYMBYAX—SYMBYAX therapy yielded steady-state concentrations of norfluoxetine similar to those seen with fluoxetine in the therapeutic dose range.

Olanzapine—Olanzapine displays linear pharmacokinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr). Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (*see* Special Populations).

Following a single oral dose of ^{14}C-labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4′-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and CYP450-mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYP1A2, CYP2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6-mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Fluoxetine—Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Fluoxetine is extensively metabolized in the liver to its only identified active metabolite, norfluoxetine, via the CYP2D6 pathway. A number of unidentified metabolites exist.

In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism and Elimination—The complexity of the metabolism of fluoxetine has several consequences that may potentially affect the clinical use of SYMBYAX.

Variability in metabolism—A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme CYP2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants (TCAs). In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative nonsaturable pathways (non-CYP2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because the metabolism of fluoxetine, like that of a number of other compounds including TCAs and other selective serotonin antidepressants, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (*see* PRECAUTIONS, Drug Interactions).

Accumulation and slow elimination—The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because the metabolism of fluoxetine is not proportional to dose. However, norfluoxetine appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine.

Special Populations

Geriatric—Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in geriatric patients. Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.

In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly subjects (>65 years of age) than in non-elderly subjects (≤65 years of age).

The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Renal Impairment—The pharmacokinetics of SYMBYAX has not been studied in patients with renal impairment. However, olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required.

Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on olanzapine metabolite elimination has not been studied.

In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Hepatic Impairment—Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment (*see* PRECAUTIONS, Use in Patients with Concomitant Illness *and* DOSAGE AND ADMINISTRATION, Special Populations).

Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (N=6) with clinically significant cirrhosis (Childs-Pugh Classification A and B) revealed little effect on the pharmacokinetics of olanzapine.

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects.

Gender—Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status—Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely required.

Race—No SYMBYAX pharmacokinetic study was conducted to investigate the effects of race. Results from an olanzapine cross-study comparison between data obtained in Japan and data obtained in the US suggest that exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are administered. Olanzapine clinical study safety and efficacy data, however, did not suggest clinically significant differences among Caucasian patients, patients of African descent, and a 3rd pooled category including Asian and Hispanic patients. Dosage modifications for race, therefore, are not routinely required.

Combined Effects—The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance of olanzapine in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. SYMBYAX dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of the olanzapine component (*see* DOSAGE AND ADMINISTRATION, Special Populations).

CLINICAL STUDIES

The efficacy of SYMBYAX for the treatment of depressive episodes associated with bipolar disorder was established in 2 identically designed, 8-week, randomized, double-blind, controlled studies of patients who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for Bipolar I Disorder, Depressed utilizing flexible dosing of SYMBYAX (6/25, 6/50, or 12/50 mg/day), olanzapine (5 to 20 mg/day), and placebo. These studies included patients (≥18 years of age) with or without psychotic symptoms and with or without a rapid cycling course.

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies was the change from baseline to endpoint in the MADRS total score. In both studies, SYMBYAX was statistically significantly superior to both olanzapine monotherapy and placebo in reduction of the MADRS total score. The results of the studies are summarized below (Table 1).

Table 1: MADRS Total Score Mean Change from Baseline to Endpoint

	Treatment Group	Baseline Mean	Change to Endpoint Mean[1]
Study 1	SYMBYAX (N=40)	30	–16[a]
	Olanzapine (N=182)	32	–12
	Placebo (N=181)	31	–10
Study 2	SYMBYAX (N=42)	32	–18[a]
	Olanzapine (N=169)	33	–14
	Placebo (N=174)	31	–9

[1] Negative number denotes improvement from baseline.

[a] Statistically significant compared to both olanzapine and placebo.

INDICATIONS AND USAGE

SYMBYAX is indicated for the treatment of depressive episodes associated with bipolar disorder. The efficacy of SYMBYAX was established in 2 identically designed, 8-week, randomized, double-blind clinical studies.

Unlike with unipolar depression, there are no established guidelines for the length of time patients with bipolar disorder experiencing a major depressive episode should be treated with agents containing antidepressant drugs.

The effectiveness of SYMBYAX for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient.

CONTRAINDICATIONS

Hypersensitivity—SYMBYAX is contraindicated in patients with a known hypersensitivity to the product or any component of the product.

Monoamine Oxidase Inhibitors (MAOI)—There have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with an MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, SYMBYAX should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses (*see* CLINICAL PHARMACOLOGY, Accumulation and slow elimination)] should be allowed after stopping SYMBYAX before starting an MAOI.

Thioridazine—Thioridazine should not be administered with SYMBYAX or administered within a minimum of 5 weeks after discontinuation of SYMBYAX (*see* WARNINGS, Thioridazine).

Continued on next page

This product information was prepared in June 2005. Current information on products of Eli Lilly and Company may be obtained by calling 1-800-545-5979.

Symbyax—Cont.

WARNINGS

Clinical Worsening and Suicide Risk—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with SYMBYAX, for a description of the risks of discontinuation of SYMBYAX).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SYMBYAX should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

It should be noted that SYMBYAX is not approved for use in treating any indications in the pediatric population.

Screening Patients for Bipolar Disorder—A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SYMBYAX is approved for use in treating bipolar depression.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis (*see* BOX WARNING).

In olanzapine placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively). Risk factors that may predispose this patient population to increased mortality when treated with olanzapine include age ≥80 years, sedation, concomitant use of benzodiazepines or presence of pulmonary conditions (e.g., pneumonia, with or without aspiration).

Cerebrovascular Adverse Events (CVAE), Including Stroke, in Elderly Patients with Dementia-Related Psychosis—Cerebrovascular Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and Diabetes Mellitus—Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Orthostatic Hypotension—SYMBYAX may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial dose-titration period.

In the bipolar depression studies, statistically significantly more orthostatic changes occurred with the SYMBYAX group compared to placebo and olanzapine groups. Orthostatic systolic blood pressure decrease of at least 30 mm Hg occurred in 7.3% (6/82), 1.4% (5/346), and 1.4% (5/352) of the SYMBYAX, olanzapine and placebo groups, respectively. Among the group of controlled clinical studies with SYMBYAX, an orthostatic systolic blood pressure decrease of ≥30 mm Hg occurred in 4% (21/512) of SYMBYAX-treated patients, 5% (10/204) of fluoxetine-treated patients, 2% (16/644) of olanzapine-treated patients, and 2% (8/445) of placebo-treated patients. In this group of studies, the incidence of syncope in SYMBYAX-treated patients was 0.4% (2/571) compared to placebo 0.2% (1/477).

In a clinical pharmacology study of SYMBYAX, three healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2 to 9 hours following a single 12-mg/50-mg dose of SYMBYAX. Reactions consisting of this combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in at least three other healthy subjects treated with various formulations of olanzapine (one oral, two intramuscular). In controlled clinical studies, the incidence of patients with a ≥20 bpm decrease in orthostatic pulse concomitantly with a ≥20 mm Hg decrease in orthostatic systolic blood pressure was 0.4% (2/549) in the SYMBYAX group, 0.2% (1/455) in the placebo group, 0.8% (5/659) in the olanzapine group, and 0% (0/241) in the fluoxetine group.

SYMBYAX should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Allergic Events and Rash—In SYMBYAX premarketing controlled clinical studies, the overall incidence of rash or allergic events in SYMBYAX-treated patients [4.6% (26/571)] was similar to that of placebo [5.2% (25/477)]. The majority of the cases of rash and/or urticaria were mild; however, three patients discontinued (one due to rash, which was moderate in severity, and two due to allergic events, one of which included face edema).

In fluoxetine US clinical studies, 7% of 10,782 fluoxetine-treated patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical studies, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In fluoxetine premarketing clinical studies, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possible allergic phenomena for which an alternative etiology cannot be identified, SYMBYAX should be discontinued.

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia—A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

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PRECAUTIONS

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The incidence of dyskinetic movement in SYMBYAX-treated patients was infrequent. The mean score on the Abnormal Involuntary Movement Scale (AIMS) across clinical studies involving SYMBYAX-treated patients decreased from baseline. Nonetheless, SYMBYAX should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on SYMBYAX, drug discontinuation should be considered. However, some patients may require treatment with SYMBYAX despite the presence of the syndrome. The need for continued treatment should be reassessed periodically.

Thioridazine—In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs that inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (*see* PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QT_c interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism (*see* CONTRAINDICATIONS, Thioridazine).

PRECAUTIONS

General

Concomitant Use of Olanzapine and Fluoxetine Products—SYMBYAX contains the same active ingredients that are in Zyprexa and Zyprexa Zydis (olanzapine) and in Prozac, Prozac Weekly, and Sarafem (fluoxetine HCl). Caution should be exercised when prescribing these medications concomitantly with SYMBYAX.

Abnormal Bleeding—Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (*see* DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of SYMBYAX with NSAIDs, aspirin, or other drugs that affect coagulation.

Mania/Hypomania—In the two controlled bipolar depression studies there was no statistically significant difference in the incidence of manic events (manic reaction or manic depressive reaction) between SYMBYAX- and placebo-treated patients. In one of the studies, the incidence of manic events was (7% [3/43]) in SYMBYAX-treated patients compared to (3% [5/184]) in placebo-treated patients. In the other study, the incidence of manic events was (2% [1/43]) in SYMBYAX-treated patients compared to (8% [15/193]) in placebo-treated patients. This limited controlled trial experience of SYMBYAX in the treatment of bipolar depression makes it difficult to interpret these findings until additional data is obtained. Because of this and the cyclical nature of bipolar disorder, patients should be monitored closely for the development of symptoms of mania/hypomania during treatment with SYMBYAX.

Body Temperature Regulation—Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs. Appropriate care is advised when prescribing SYMBYAX for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

Cognitive and Motor Impairment—Somnolence was a commonly reported adverse event associated with SYMBYAX treatment, occurring at an incidence of 22% in SYMBYAX patients compared with 11% in placebo patients. Somnolence led to discontinuation in 2% (10/571) of patients in the premarketing controlled clinical studies.

As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely.

Discontinuation of Treatment with SYMBYAX

During marketing of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with fluoxetine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug (*see* DOSAGE AND ADMINISTRATION).

Dysphagia—Dysphagia was observed infrequently in SYMBYAX-treated patients in premarketing clinical studies. Nonetheless, like other psychotropic drugs, SYMBYAX should be used cautiously in patients at risk for aspiration pneumonia.

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease.

Half-Life—Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* CLINICAL PHARMACOLOGY, Accumulation and slow elimination).

Hyperprolactinemia—As with other drugs that antagonize dopamine D_2 receptors, SYMBYAX elevates prolactin levels, and a modest elevation persists during administration; however, possibly associated clinical manifestations (e.g., galactorrhea and breast enlargement) were infrequently observed.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds that increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Hyponatremia—Hyponatremia has been observed in SYMBYAX premarketing clinical studies. In controlled trials, no SYMBYAX-treated patients had a treatment-emergent serum sodium below 130 mmol/L; however, a lowering of serum sodium below the reference range occurred at an incidence of 2% (10/500) of SYMBYAX patients compared with 0.5% (2/380) of placebo patients. In open label studies, 0.3% (5/1889) of these SYMBYAX-treated patients had a treatment-emergent serum sodium below 130 mmol/L.

Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported with fluoxetine. The hyponatremia appeared to be reversible when fluoxetine was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two 6-week controlled studies in patients ≥60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

Seizures—Seizures occurred in 0.2% (4/2066) of SYMBYAX-treated patients during open-label premarketing clinical studies. No seizures occurred in the premarketing controlled SYMBYAX studies. Seizures have also been reported with both olanzapine and fluoxetine monotherapy. Therefore, SYMBYAX should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of ≥65 years of age.

Transaminase Elevations—As with olanzapine, asymptomatic elevations of hepatic transaminases [ALT (SGPT), AST (SGOT), and GGT] and alkaline phosphatase have been observed with SYMBYAX. In the SYMBYAX-controlled database, ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 6.3% (31/495) of patients exposed to SYMBYAX compared with 0.5% (2/384) of the placebo patients and 4.5% (25/560) of olanzapine-treated patients. The difference between SYMBYAX and placebo was statistically significant. None of these 31 SYMBYAX-treated patients experienced jaundice and three had transient elevations >200 IU/L.

In olanzapine placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared with 0% (0/115) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment, and in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger olanzapine premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued. Among all 2500 patients in olanzapine clinical studies, approximately 1% (23/2500) discontinued treatment due to transaminase increases.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Laboratory Tests).

Weight Gain—In clinical studies, the mean weight increase for SYMBYAX-treated patients was statistically significantly greater than placebo-treated (3.6 kg vs -0.3 kg) and fluoxetine-treated (3.6 kg vs -0.7 kg) patients, but was not statistically significantly different from olanzapine-treated patients (3.6 kg vs 3.0 kg). Fourteen percent of SYMBYAX-treated patients met criterion for having gained >10% of their baseline weight. This was statistically significantly greater than placebo-treated (<1%) and fluoxetine-treated patients (<1%) but was not statistically significantly different than olanzapine-treated patients (11%).

Use in Patients with Concomitant Illness

Clinical experience with SYMBYAX in patients with concomitant systemic illnesses is limited (*see* CLINICAL PHARMACOLOGY, Renal Impairment *and* Hepatic Impairment). The following precautions for the individual components may be applicable to SYMBYAX.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical studies, SYMBYAX was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for study discontinuations; SYMBYAX should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, a history of paralytic ileus, or related conditions.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse events were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%).

As with other CNS-active drugs, SYMBYAX should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (*see* BOX WARNING *and* WARNINGS).

SYMBYAX has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the premarket testing.

Caution is advised when using SYMBYAX in cardiac patients and in patients with diseases or conditions that could affect hemodynamic responses (*see* WARNINGS, Orthostatic Hypotension).

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower dose of the fluoxetine component of SYMBYAX should be used in patients with cirrhosis. Caution is advised when using SYMBYAX in patients with diseases or conditions that could affect its metabolism (*see* CLINICAL PHARMACOLOGY, Hepatic Impairment *and* DOSING AND ADMINISTRATION, Special Populations).

Olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required (*see* CLINICAL PHARMACOLOGY, Renal Impairment).

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SYMBYAX and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for SYMBYAX. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Continued on next page

This product information was prepared in June 2005. Current information on products of Eli Lilly and Company may be obtained by calling 1-800-545-5979.

Symbyax—Cont.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SYMBYAX.

Clinical Worsening and Suicide Risk—Patients their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Abnormal Bleeding—Patients should be cautioned about the concomitant use of SYMBYAX and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding (*see* PRECAUTIONS, Abnormal Bleeding).

Alcohol—Patients should be advised to avoid alcohol while taking SYMBYAX.

Cognitive and Motor Impairment—As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely.

Concomitant Medication—Patients should be advised to inform their physician if they are taking Prozac®, Prozac Weekly™, Sarafem®, fluoxetine, Zyprexa®, or Zyprexa Zydis®. Patients should also be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions.

Heat Exposure and Dehydration—Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Nursing—Patients, if taking SYMBYAX, should be advised not to breast-feed.

Orthostatic Hypotension—Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol (*see* WARNINGS *and* Drug Interactions).

Pregnancy—Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during SYMBYAX therapy.

Rash—Patients should be advised to notify their physician if they develop a rash or hives while taking SYMBYAX.

Treatment Adherence—Patients should be advised to take SYMBYAX exactly as prescribed, and to continue taking SYMBYAX as prescribed even after their mood symptoms improve. Patients should be advised that they should not alter their dosing regimen, or stop taking SYMBYAX, without consulting their physician.

Patient information is printed at the end of this insert. Physicians should discuss this information with their patients and instruct them to read the Medication Guide before starting therapy with SYMBYAX and each time their prescription is refilled.

Laboratory Tests

Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Transaminase Elevations).

Drug Interactions

The risks of using SYMBYAX in combination with other drugs have not been extensively evaluated in systematic studies. The drug-drug interactions of the individual components are applicable to SYMBYAX. As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility. Caution is advised if the concomitant administration of SYMBYAX and other CNS-active drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (*see* CLINICAL PHARMACOLOGY, Accumulation and slow elimination).

Antihypertensive agents—Because of the potential for olanzapine to induce hypotension, SYMBYAX may enhance the effects of certain antihypertensive agents (*see* WARNINGS, Orthostatic Hypotension).

Anti-Parkinsonian—The olanzapine component of SYMBYAX may antagonize the effects of levodopa and dopamine agonists.

Benzodiazepines—Multiple doses of olanzapine did not influence the pharmacokinetics of diazepam and its active metabolite N-desmethyldiazepam. However, the coadministration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine.

When concurrently administered with fluoxetine, the half-life of diazepam may be prolonged in some patients (*see* CLINICAL PHARMACOLOGY, Accumulation and slow elimination). Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Biperiden—Multiple doses of olanzapine did not influence the pharmacokinetics of biperiden.

Carbamazepine—Carbamazepine therapy (200 mg BID) causes an approximate 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Patients on stable doses of carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Clozapine—Elevation of blood levels of clozapine has been observed in patients receiving concomitant fluoxetine.

Electroconvulsive therapy (ECT)—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment (*see* Seizures).

Ethanol—Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The coadministration of ethanol with SYMBYAX may potentiate sedation and orthostatic hypotension.

Fluvoxamine—Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine administration of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of the olanzapine component of SYMBYAX should be considered in patients receiving concomitant treatment with fluvoxamine.

Haloperidol—Elevation of blood levels of haloperidol has been observed in patients receiving concomitant fluoxetine.

Lithium—Multiple doses of olanzapine did not influence the pharmacokinetics of lithium.

There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored in patients taking SYMBYAX concomitantly with lithium.

Monoamine oxidase inhibitors—*See* CONTRAINDICATIONS.

Phenytoin—Patients on stable doses of phenytoin have developed elevated plasma levels of phenytoin with clinical phenytoin toxicity following initiation of concomitant fluoxetine.

Pimozide—A single case report has suggested possible additive effects of pimozide and fluoxetine leading to bradycardia.

Sumatriptan—There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) is clinically warranted, appropriate observation of the patient is advised.

Theophylline—Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

Thioridazine—*See* CONTRAINDICATIONS *and* WARNINGS, Thioridazine.

Tricyclic antidepressants (TCAs)—Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

In two fluoxetine studies, previously stable plasma levels of imipramine and desipramine have increased >2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when SYMBYAX is coadministered or has been recently discontinued (*see* Drugs metabolized by CYP2D6 *and* CLINICAL PHARMACOLOGY, Accumulation and slow elimination).

Tryptophan—Five patients receiving fluoxetine in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Valproate—In vitro studies using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Warfarin—Warfarin (20-mg single dose) did not affect olanzapine pharmacokinetics. Single doses of olanzapine did not affect the pharmacokinetics of warfarin.

Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin (*see* PRECAUTIONS, Abnormal Bleeding). Patients receiving warfarin therapy should receive careful coagulation monitoring when SYMBYAX is initiated or stopped.

Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.)—Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding (*see* PRECAUTIONS, Abnormal Bleeding). Thus, patients should be cautioned about the use of such drugs concurrently with SYMBYAX.

Drugs metabolized by CYP2D6—In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP2D6. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by this enzyme.

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6. Such individuals have been referred to as poor metabolizers of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most antidepressants, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite, the sum of the plasma concentrations of the 4 enantiomers is comparable between poor and extensive metabolizers (*see* CLINICAL PHARMACOLOGY, Variability in metabolism).

Fluoxetine, like other agents that are metabolized by CYP2D6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble poor metabolizers. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous five weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (including but not limited to, flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated thioridazine plasma levels, thioridazine should not be administered with fluoxetine or within a minimum of five weeks after fluoxetine has been discontinued (*see* CONTRAINDICATIONS, Monoamine Oxidase Inhibitors (MAOI) *and* WARNINGS, Thioridazine).

Drugs metabolized by CYP3A—In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

In an in vivo interaction study involving the coadministration of fluoxetine with single doses of terfenadine (a CYP3A substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A activity is not likely to be of clinical significance.

Effect of olanzapine on drugs metabolized by other CYP enzymes—In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, and CYP2C19. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

The effect of other drugs on olanzapine—Fluoxetine, an inhibitor of CYP2D6, decreases olanzapine clearance a small amount (*see* CLINICAL PHARMACOLOGY, Pharmacokinetics). Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Fluvoxamine, an inhibitor of CYP1A2, decreases olanzapine clearance (*see* Drug Interactions, Fluvoxamine). The effect of CYP1A2 inhibitors, such as fluvoxamine and some fluoroquinolone antibiotics, on SYMBYAX has not been evaluated. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

Drugs tightly bound to plasma proteins—The in vitro binding of SYMBYAX to human plasma proteins is similar to the individual components. The interaction between SYMBYAX and other highly protein-bound drugs has not been fully evaluated. Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (*see* CLINICAL PHARMACOLOGY, Distribution *and* PRECAUTIONS, Drug Interactions).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity, or fertility studies were conducted with SYMBYAX. The following data are based on findings in studies performed with the individual components.

Carcinogenesis

Olanzapine—Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, and 30/20 mg/kg/day [equivalent to 0.8 to 5 times the maximum recommended human daily dose (MRHD) on a mg/m^2 basis] and 0.25, 2

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and 8 mg/kg/day (equivalent to 0.06 to 2 times the MRHD on a mg/m^2 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, and 4 mg/kg/day (males) and 0.25, 1, 4, and 8 mg/kg/day (females) (equivalent to 0.1 to 2 and 0.1 to 4 times the MRHD on a mg/m^2 basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in females dosed at 8 mg/kg/day (2 times the MRHD on a mg/m^2 basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2 to 5 times the MRHD on a mg/m^2 basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the MRHD on a mg/m^2 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the finding of prolactin-mediated endocrine tumors in rodents is unknown (*see* PRECAUTIONS, Hyperprolactinemia).

Fluoxetine—The dietary administration of fluoxetine to rats and mice for two years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the MRHD on a mg/m^2 basis), produced no evidence of carcinogenicity.

Mutagenesis

Olanzapine—No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Fluoxetine—Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility

SYMBYAX—Fertility studies were not conducted with SYMBYAX. However, in a repeat-dose rat toxicology study of three months duration, ovary weight was decreased in females treated with the low-dose [2 and 4 mg/kg/day (1 and 0.5 times the MRHD on a mg/m^2 basis), respectively] and high-dose [4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m^2 basis), respectively] combinations of olanzapine and fluoxetine. Decreased ovary weight, and corpora luteal depletion and uterine atrophy were observed to a greater extent in the females receiving the high-dose combination than in females receiving either olanzapine or fluoxetine alone. In a 3-month repeat-dose dog toxicology study, reduced epididymal sperm and reduced testicular and prostate weights were observed with the high-dose combination of olanzapine and fluoxetine [5 and 5 mg/kg/day (9 and 2 times the MRHD on a mg/m^2 basis), respectively] and with olanzapine alone (5 mg/kg/day or 9 times the MRHD on a mg/m^2 basis).

Olanzapine—In a fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the MRHD on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male-mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the MRHD on a mg/m^2 basis). Diestrous was prolonged and estrous was delayed at 1.1 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis); therefore, olanzapine may produce a delay in ovulation.

Fluoxetine—Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility (*see* ANIMAL TOXICOLOGY).

Pregnancy — Pregnancy Category C

SYMBYAX

Embryo fetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine in low-dose and high-dose combinations. In rats, the doses were: 2 and 4 mg/kg/day (low-dose) [1 and 0.5 times the MRHD on a mg/m^2 basis, respectively], and 4 and 8 mg/kg/day (high-dose) [2 and 1 times the MRHD on a mg/m^2 basis, respectively]. In rabbits, the doses were 4 and 4 mg/kg/day (low-dose) [4 and 1 times the MRHD on a mg/m^2 basis, respectively], and 8 and 8 mg/kg/day (high-dose) [9 and 2 times the MRHD on a mg/m^2 basis, respectively]. In these studies, olanzapine and fluoxetine were also administered alone at the high-doses (4 and 8 mg/kg/day, respectively, in the rat; 8 and 8 mg/kg/day, respectively, in the rabbit). In the rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced decreases in fetal weight and retarded skeletal ossification in conjunction with maternal toxicity. Similarly, in the rat there was no evidence of teratogenicity; however, a decrease in fetal weight was observed with the high-dose combination.

In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were administered during pregnancy and throughout lactation in combination (low-dose: 2 and 4 mg/kg/day [1 and 0.5 times the MRHD on a mg/m^2 basis], respectively, high-dose: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively, and alone: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively). Administration of the high-dose combination resulted in a marked elevation in offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone. These effects were not observed with the low-dose combination; however, there were a few cases of testicular degeneration and atrophy, depletion of epididymal sperm and infertility in the male progeny. The effects of the high-dose combination on postnatal endpoints could not be assessed due to high progeny mortality.

There are no adequate and well-controlled studies with SYMBYAX in pregnant women.

SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Olanzapine

In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/m^2 basis, respectively), no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m^2 basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled clinical studies with olanzapine in pregnant women. Seven pregnancies were observed during premarketing clinical studies with olanzapine, including two resulting in normal births, one resulting in neonatal death due to a cardiovascular defect, three therapeutic abortions, and one spontaneous abortion.

Fluoxetine

In embryo fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the MRHD on a mg/m^2 basis, respectively) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis).

Nonteratogenic Effects—Neonates exposed to fluoxetine and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (*see* CONTRAINDICATIONS, Monoamine Oxidase Inhibitors). When treating a pregnant woman with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (*see* DOSAGE AND ADMINISTRATION).

Labor and Delivery

SYMBYAX

The effect of SYMBYAX on labor and delivery in humans is unknown. Parturition in rats was not affected by SYMBYAX. SYMBYAX should be used during labor and delivery only if the potential benefit justifies the potential risk.

Olanzapine

Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

Fluoxetine

The effect of fluoxetine on labor and delivery in humans is unknown. Fluoxetine crosses the placenta; therefore, there is a possibility that fluoxetine may have adverse effects on the newborn.

Nursing Mothers

SYMBYAX

There are no adequate and well-controlled studies with SYMBYAX in nursing mothers or infants. No studies have been conducted to examine the excretion of olanzapine or fluoxetine in breast milk following SYMBYAX treatment. It is recommended that women not breast-feed when receiving SYMBYAX.

Olanzapine

Olanzapine was excreted in milk of treated rats during lactation.

Fluoxetine

Fluoxetine is excreted in human breast milk. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the 2nd day of feeding.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (*see* BOX WARNING *and* WARNINGS, Clinical Worsening and Suicide Risk *and* ANIMAL TOXICOLOGY). Anyone considering the use of SYMBYAX in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use

SYMBYAX

Clinical studies of SYMBYAX did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (*see* DOSAGE AND ADMINISTRATION).

Olanzapine

Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263 patients) were ≥65 years of age. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared with younger patients. Studies in patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared with younger patients with schizophrenia. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (*see* BOX WARNING, WARNINGS, PRECAUTIONS, Use in Patients with Concomitant Illness *and* DOSAGE AND ADMINISTRATION, Special Populations).

As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient.

Fluoxetine

US fluoxetine clinical studies (10,782 patients) included 687 patients ≥65 years of age and 93 patients ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients.

ADVERSE REACTIONS

The information below is derived from a premarketing clinical study database for SYMBYAX consisting of 2066 patients with various diagnoses with approximately 1061 patient-years of exposure. The conditions and duration of treatment with SYMBYAX varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or long-term exposure.

Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The data in the tables represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is possible that events reported during therapy were not necessarily related to drug exposure. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments,

Continued on next page

This product information was prepared in June 2005. Current information on products of Eli Lilly and Company may be obtained by calling 1-800-545-5979.

Symbyax—Cont.

uses, and investigators. The cited figures, however, do provide the prescribing clinician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Incidence in Controlled Clinical Studies

The following findings are based on the short-term, controlled premarketing studies in various diagnoses including bipolar depression.

Adverse events associated with discontinuation of treatment—Overall, 10% of the patients in the SYMBYAX group discontinued due to adverse events compared with 4.6% for placebo. Table 2 enumerates the adverse events leading to discontinuation associated with the use of SYMBYAX (incidence of at least 1% for SYMBYAX and greater than that for placebo). The bipolar depression column shows the incidence of adverse events with SYMBYAX in the bipolar depression studies and the "SYMBYAX-Controlled" column shows the incidence in the controlled SYMBYAX studies; the placebo column shows the incidence in the pooled controlled studies that included a placebo arm.

Table 2: Adverse Events Associated with Discontinuation*

Adverse Event	Percentage of Patients Reporting Event		
	SYMBYAX		Placebo
	Bipolar Depression (N=86)	SYMBYAX-Controlled (N=571)	(N=477)
Asthenia	0	1	0
Somnolence	0	2	0
Weight gain	0	2	0
Chest pain	1	0	0

*Table includes events associated with discontinuation of at least 1% and greater than placebo

Commonly observed adverse events in controlled clinical studies—The most commonly observed adverse events associated with the use of SYMBYAX (incidence of ≥5% and at least twice that for placebo in the SYMBYAX-controlled database) were: asthenia, edema, increased appetite, peripheral edema, pharyngitis, somnolence, thinking abnormal, tremor, and weight gain.

Adverse events occurring at an incidence of 2% or more in controlled clinical studies—Table 3 enumerates the treatment-emergent adverse events associated with the use of SYMBYAX (incidence of at least 2% for SYMBYAX and twice or more that for placebo).

Table 3: Treatment-Emergent Adverse Events: Incidence in Controlled Clinical Studies

Body System/ Adverse Event[1]	Percentage of Patients Reporting Event		
	SYMBYAX		Placebo
	Bipolar Depression (N=86)	SYMBYAX-Controlled (N=571)	(N=477)
Body as a Whole			
Asthena	13	15	3
Accidental injury	5	3	2
Fever	4	3	1
Cardiovascular System			
Hypertension	2	2	1
Tachycardia	2	2	0
Digestive System			
Diarrhea	19	8	7
Dry Mouth	16	11	6
Increased appetite	13	16	4
Tooth disorder	1	2	1
Metabolic and Nutritional Disorders			
Weight gain	17	21	3
Peripheral edema	4	8	1
Edema	0	5	0
Musculoskeletal System			
Joint disorder	1	2	1
Twitching	6	2	1
Arthralgia	5	3	1
Nervous System			
Somnolence	21	22	11
Tremor	9	8	3
Thinking abnormal	6	6	3
Libido decreased	4	2	1
Hyperkinesia	2	1	1
Personality disorder	2	1	1
Sleep disorder	2	1	1
Amnesia	1	3	0
Respiratory System			
Pharyngitis	4	6	3
Dyspnea	1	2	1
Special Senses			
Ambylopia	5	4	2
Ear pain	2	1	1
Otitis media	2	0	0
Speech disorder	0	2	0
Urogenital System			
Abnormal ejaculation[2]	7	2	1
Impotence[2]	4	2	1
Anorgasmia	3	1	0

[1] Included are events reported by at least 2% of patients taking SYMBYAX except the following events, which had an incidence on placebo ≥ SYMBYAX: abdominal pain, abnormal dreams, agitation, akathisia, anorexia, anxiety, apathy, back pain, chest pain, constipation, cough increased, depression, dizziness, dysmenorrhea[2], dyspepsia, flatulence, flu syndrome, headache, hypertonia, insomnia, manic reaction, myalgia, nausea, nervousness, pain, palpitation, paresthesia, rash, rhinitis, sinusitis, sweating, vomiting.

[2] Adjusted for gender.

Additional Findings Observed in Clinical Studies

The following findings are based on clinical studies.

Effect on cardiac repolarization—The mean increase in QT_c interval for SYMBYAX-treated patients (4.9 msec) in clinical studies was significantly greater than that for placebo-treated (-0.9 msec) and olanzapine-treated (0.6 msec) patients, but was not significantly different from fluoxetine-treated (3.7 msec) patients. There were no differences between patients treated with SYMBYAX, placebo, olanzapine, or fluoxetine in the incidence of QT_c outliers (>500 msec).

Laboratory changes—In SYMBYAX clinical studies, SYMBYAX was associated with asymptomatic mean increases in alkaline phosphatase, cholesterol, GGT, and uric acid compared with placebo (*see* PRECAUTIONS, Transaminase Elevations).

SYMBYAX was associated with a slight decrease in hemoglobin that was statistically significantly greater than that seen with placebo, olanzapine, and fluoxetine.

An elevation in serum prolactin was observed with SYMBYAX. This elevation was not statistically different than that seen with olanzapine (*see* PRECAUTIONS, Hyperprolactinemia).

In olanzapine clinical studies among olanzapine-treated patients with random triglyceride levels of <150 mg/dL at baseline (N=485), 0.6% of patients experienced triglyceride levels of ≥500 mg/dL anytime during the studies. In these same studies, olanzapine-treated patients (N=962) had a mean increase of 27 mg/dL in triglycerides from a mean baseline value of 185 mg/dL.

In olanzapine placebo-controlled studies, olanzapine-treated patients with random cholesterol levels of <200 mg/dL at baseline (N=1439) experienced cholesterol levels of ≥240 mg/dL anytime during the studies significantly more often than placebo-treated patients (N=836) (8.1% vs 3.8%, respectively). In these same studies, olanzapine-treated patients (N=2528) had a mean increase of 1 mg/dL in cholesterol from a mean baseline value of 203 mg/dL, which was significantly different compared to placebo-treated patients (N=1420) with a mean decrease of 4 mg/dL from a mean baseline value of 203 mg/dL.

Sexual dysfunction—In the pool of controlled SYMBYAX studies, there were higher rates of the treatment-emergent adverse events decreased libido, anorgasmia, impotence and abnormal ejaculation in the SYMBYAX group than in the placebo group. One case of decreased libido led to discontinuation in the SYMBYAX group. In the controlled studies that contained a fluoxetine arm, the rates of decreased libido and abnormal ejaculation in the SYMBYAX group were less than the rates in the fluoxetine group. None of the differences were statistically significant.

Sexual dysfunction, including priapism, has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital signs—Tachycardia, bradycardia, and orthostatic hypotension have occurred in SYMBYAX-treated patients (*see* WARNINGS, Orthostatic Hypotension). The mean pulse of SYMBYAX-treated patients was reduced by 1.6 beats/min.

Other Events Observed in Clinical Studies

Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking SYMBYAX in clinical studies except (1) those listed in the body or footnotes of Tables 2 and 3 above or elsewhere in labeling, (2) those for which the COSTART terms were uninformative or misleading, (3) those events for which a causal relationship to SYMBYAX use was considered remote, and (4) events occurring in only 1 patient treated with SYMBYAX and which did not have a substantial probability of being acutely life-threatening.

Events are classified within body system categories using the following definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients, infrequent adverse events are those occurring in 1/100 to 1/1000 patients, and rare events are those occurring in <1/1000 patients.

Body as a Whole—*Frequent:* chills, infection, neck pain, neck rigidity, photosensitivity reaction; *Infrequent:* cellulitis, cyst, hernia, intentional injury, intentional overdose, malaise, moniliasis, overdose, pelvic pain, suicide attempt; *Rare:* death, tolerance decreased.

Cardiovascular System—*Frequent:* migraine, vasodilatation; *Infrequent:* arrhythmia, bradycardia, cerebral ischemia, electrocardiogram abnormal, hypotension, QT-interval prolonged; *Rare:* angina pectoris, atrial arrhythmia, atrial fibrillation, bundle branch block, congestive heart failure, myocardial infarct, peripheral vascular disorder, T-wave inverted.

Digestive System—*Frequent:* increased salivation, thirst; *Infrequent:* cholelithiasis, colitis, eructation, esophagitis, gastritis, gastroenteritis, gingivitis, hepatomegaly, nausea and vomiting, peptic ulcer, periodontal abscess, stomatitis, tooth caries; *Rare:* aphthous stomatitis, fecal incontinence, gastrointestinal hemorrhage, gum hemorrhage, intestinal obstruction, liver fatty deposit, pancreatitis.

Endocrine System—*Infrequent:* hypothyroidism.

Hemic and Lymphatic System—*Frequent:* ecchymosis; *Infrequent:* anemia, leukocytosis, lymphadenopathy; *Rare:* coagulation disorder, leukopenia, purpura, thrombocythemia.

Metabolic and Nutritional—*Frequent:* generalized edema, weight loss; *Infrequent:* alcohol intolerance, dehydration, glycosuria, hyperlipemia, hypoglycemia, hypokalemia, obesity; *Rare:* acidosis, bilirubinemia, creatinine increased, gout, hyperkalemia, hypoglycemic reaction.

Musculoskeletal System—*Infrequent:* arthritis, bone disorder, generalized spasm, leg cramps, tendinous contracture, tenosynovitis; *Rare:* arthrosis, bursitis, myasthenia, myopathy, osteoporosis, rheumatoid arthritis.

Nervous System—*Infrequent:* abnormal gait, ataxia, buccoglossal syndrome, cogwheel rigidity, coma, confusion, depersonalization, dysarthria, emotional lability, euphoria, extrapyramidal syndrome, hostility, hypesthesia, hypokinesia, incoordination, movement disorder, myoclonus, neuralgia, neurosis, vertigo; *Rare:* acute brain syndrome, aphasia, dystonia, libido increased, subarachnoid hemorrhage, withdrawal syndrome.

Respiratory System—*Frequent:* bronchitis, lung disorder; *Infrequent:* apnea, asthma, epistaxis, hiccup, hyperventilation, laryngitis, pneumonia, voice alteration, yawn; *Rare:* emphysema, hemoptysis, laryngismus.

Skin and Appendages—*Infrequent:* acne, alopecia, contact dermatitis, dry skin, eczema, pruritis, psoriasis, skin discoloration, vesiculobullous rash; *Rare:* exfoliative dermatitis, maculopapular rash, seborrhea, skin ulcer.

Special Senses—*Frequent:* abnormal vision, taste perversion, tinnitus; *Infrequent:* abnormality of accommodation, conjunctivitis, deafness, diplopia, dry eyes, eye pain, miosis; *Rare:* eye hemorrhage.

Urogenital System—*Frequent:* breast pain, menorrhagia[1], urinary frequency, urinary incontinence, urinary tract infection; *Infrequent:* amenorrhea[1], breast enlargement, breast neoplasm, cystitis, dysuria, female lactation[1], fibrocystic breast[1]; hematuria, hypomenorrhea[1], leukorrhea[1], menopause[1], metrorrhagia[1], oliguria, ovarian disorder[1], polyuria, urinary retention, urinary urgency, urination impaired, vaginal hemorrhage[1], vaginal moniliasis[1], vaginitis[1]; *Rare:* breast carcinoma, breast engorgement, endometrial diso

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Other Events Observed with Olanzapine or Fluoxetine Monotherapy

The following adverse events were not observed in SYMBYAX-treated patients during premarketing clinical studies but have been reported with olanzapine or fluoxetine monotherapy: aplastic anemia, cholestatic jaundice, diabetic coma, dyskinesia, eosinophilic pneumonia, hepatitis, idiosyncratic hepatitis, priapism, pulmonary embolism, rhabdomyolysis, serotonin syndrome, serum sickness-like reaction, sudden unexpected death, suicidal ideation, vasculitis, venous thromboembolic events (including pulmonary embolism and deep venous thrombosis), violent behaviors. Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been rarely reported.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class—SYMBYAX is not a controlled substance.

Physical and Psychological Dependence—SYMBYAX, as with fluoxetine and olanzapine, has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical studies did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SYMBYAX (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

In studies in rats and rhesus monkeys designed to assess abuse and dependence potential, olanzapine alone was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence at oral doses up to 15 (rat) and 8 (monkey) times the MRHD (20 mg) on a mg/m^2 basis.

OVERDOSAGE

SYMBYAX

During premarketing clinical studies of the olanzapine/fluoxetine combination, overdose of both fluoxetine and olanzapine were reported in five study subjects. Four of the five subjects experienced loss of consciousness (3) or coma (1). No fatalities occurred.

Since the market introduction of olanzapine in October 1996, adverse event cases involving combination use of fluoxetine and olanzapine have been reported to Eli Lilly and Company. An overdose of combination therapy is defined as confirmed or suspected ingestion of a dose of olanzapine 20 mg or greater in combination with a dose of fluoxetine 80 mg or greater. As of 1 February 2002, 12 cases of combination therapy overdose were reported, most of which involved additional substances. Adverse events associated with these reports included somnolence; impaired consciousness (coma, lethargy); impaired neurologic function (ataxia, confusion, convulsions, dysarthria); arrhythmias; and fatality. Fatalities have been confounded by exposure to additional substances including alcohol, thioridazine, oxycodone, and propoxyphene.

Olanzapine

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia as well as a patient that experienced sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

Fluoxetine

Worldwide exposure to fluoxetine is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdose, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdose were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

SYMBYAX	CAPSULE STRENGTH			
	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
Color	Mustard Yellow & Light Yellow	Mustard Yellow & Light Grey	Red & Light Yellow	Red & Light Grey
Capsule No.	PU3231	PU3233	PU3232	PU3234
Identification	Lilly 3231 6/25	Lilly 3233 6/50	Lilly 3232 12/25	Lilly 3234 12/50
NDC Codes				
Bottles 30	0002-3231-30	0002-3233-30	0002-3232-30	0002-3234-30
Bottles 100	0002-3231-02	0002-3233-02	0002-3232-02	0002-3234-02
Bottles 1000	0002-3231-04	0002-3233-04	0002-3232-04	0002-3234-04
Blisters ID[b] 100	0002-3231-33	0002-3233-33	0002-3232-33	0002-3234-33

[a] Fluoxetine base equivalent.
[b] IDENTI-DOSE®, Unit Dose Medication, Lilly.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown outcome. One of the 6 fatalities was a 9-year-old boy who had a history of OCD, Tourette's Syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams, which was nonlethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) included coma, delirium, ECG abnormalities (such as QT-interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia, stupor, and syncope.

Management of Overdose—In managing overdose, the possibility of multiple drug involvement should be considered. In case of acute overdose, establish and maintain an airway and ensure adequate ventilation, which may include intubation. Induction of emesis is not recommended as the possibility of obtundation, seizures, or dystonic reactions of the head and neck following overdose may create a risk for aspiration. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

A specific precaution involves patients who are taking or have recently taken SYMBYAX and may have ingested excessive quantities of a TCA (tricyclic antidepressant). In such cases, accumulation of the parent TCA and/or an active metabolite may increase the possibility of serious sequelae and extend the time needed for close medical observation.

Due to the large volume of distribution of olanzapine and fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidote for either fluoxetine or olanzapine overdose is known. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Do not use epinephrine, dopamine, or other sympathomimetics with β-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.

The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR).*

DOSAGE AND ADMINISTRATION

SYMBYAX should be administered once daily in the evening, generally beginning with the 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg (*see* CLINICAL STUDIES).

The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies.

Special Populations

The starting dose of SYMBYAX 6 mg/25 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of SYMBYAX (female gender, geriatric age, nonsmoking status). When indicated, dose escalation should be performed with caution in these patients. SYMBYAX has not been systematically studied in patients over 65 years of age or in patients <18 years of age (*see* WARNINGS, Orthostatic Hypotension, PRECAUTIONS, Pediatric Use, *and* Geriatric Use, *and* CLINICAL PHARMACOLOGY, Pharmacokinetics).

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to fluoxetine, a component of SYMBYAX, and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (*see* PRECAUTIONS). When treating pregnant women with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering fluoxetine in the third trimester.

Discontinuation of Treatment with SYMBYAX

Symptoms associated with discontinuation of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs, have been reported (*see* PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy which may minimize the risk of discontinuation symptoms with this drug.

HOW SUPPLIED

SYMBYAX capsules are supplied in 6/25-, 6/50-, 12/25-, and 12/50-mg (mg equivalent olanzapine/mg equivalent fluoxetine[a]) strengths.

[See table above].

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Keep tightly closed and protect from moisture.

ANIMAL TOXICOLOGY

Fluoxetine—In a juvenile toxicology study in CD rats, administration of 30 mg/kg of fluoxetine hydrochloride on postnatal days 21 through 90 resulted in increased serum activities of creatine kinase (CK) and aspartate aminotransferase (AST), which were accompanied microscopically by skeletal muscle degeneration, necrosis and regeneration. Other findings in rats administered 30 mg/kg included degeneration and necrosis of seminiferous tubules of the testis, epididymal epithelial vacuolation, and immaturity and inactivity of the female reproductive tract. Plasma levels achieved in these animals at 30 mg/kg were approximately 5- to 8-fold (fluoxetine) and 18- to 20-fold (norfluoxetine), and at 10 mg/kg approximately 2-fold (fluoxetine) and 8-fold (norfluoxetine) higher compared to plasma concentrations usually achieved in pediatric patients. Following an approximate 11-week recovery period, sperm assessments in the 30-mg/kg males only, indicated an approximately 30% decrease in sperm concentrations without affecting sperm morphology or motility. Microscopic evaluation of testes and epididymides of these 30-mg/kg males indicated that testicular degeneration was irreversible. Delays in sexual maturation occurred in the 10-mg/kg males and in the 30-mg/kg males and females. The significance of these findings in humans is unknown. Femur lengths at 30 mg/kg increased to a lesser extent compared with control rats.

Medication Guide

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant

Continued on next page

This product information was prepared in June 2005. Current information on products of Eli Lilly and Company may be obtained by calling 1-800-545-5979.

Symbyax—Cont.

4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies,*** but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your health care provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her health care provider

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your health care provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's health care provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's health care provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her health care provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your health care provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).

Your health care provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your health care provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your health care provider or pharmacist where to find more information.

Prozac® is a registered trademark of Eli Lilly and Company.
Zoloft® is a registered trademark of Pfizer Pharmaceuticals.
Anafranil® is a registered trademark of Mallinckrodt Inc.

This Medication Guide has been approved by the US Food and Drug Administration for all antidepressants.

Rx only

Literature revised April 26, 2005
PV 4208 AMP

Shown in Product Identification Guide, page 320

XIGRIS® ℞

[zī'grĭs]

Drotrecogin alfa (activated)

DESCRIPTION

Xigris® (drotrecogin alfa (activated)) is a recombinant form of human Activated Protein C. An established human cell line possessing the complementary DNA for the inactive human Protein C zymogen secretes the protein into the fermentation medium. Fermentation is carried out in a nutrient medium containing the antibiotic geneticin sulfate. Geneticin sulfate is not detectable in the final product. Human Protein C is enzymatically activated by cleavage with thrombin and subsequently purified.

Drotrecogin alfa (activated) is a serine protease with the same amino acid sequence as human plasma-derived Activated Protein C. Drotrecogin alfa (activated) is a glycoprotein of approximately 55 kilodalton molecular weight, consisting of a heavy chain and a light chain linked by a disulfide bond. Drotrecogin alfa (activated) and human plasma-derived Activated Protein C have the same sites of glycosylation, although some differences in the glycosylation structures exist.

Xigris is supplied as a sterile, lyophilized, white to off-white powder for intravenous infusion. The 5 and 20 mg vials of Xigris contain 5.3 mg and 20.8 mg of drotrecogin alfa (activated), respectively. The 5 and 20 mg vials of Xigris also contain 40.3 and 158.1 mg of sodium chloride, 10.9 and 42.9 mg of sodium citrate, and 31.8 and 124.9 mg of sucrose, respectively.

CLINICAL PHARMACOLOGY

General Pharmacology

Activated Protein C exerts an antithrombotic effect by inhibiting Factors Va and VIIIa. *In vitro* data indicate that Activated Protein C has indirect profibrinolytic activity through its ability to inhibit plasminogen activator inhibitor-1 (PAI-1) and limiting generation of activated thrombin-activatable-fibrinolysis-inhibitor. Additionally, *in vitro* data indicate that Activated Protein C may exert an anti-inflammatory effect by inhibiting human tumor necrosis factor production by monocytes, by blocking leukocyte adhesion to selectins, and by limiting the thrombin-induced inflammatory responses within the microvascular endothelium.

Pharmacodynamics

The specific mechanisms by which Xigris exerts its effect on survival in patients with severe sepsis are not completely understood. In patients with severe sepsis, Xigris infusions of 48 or 96 hours produced dose dependent declines in D-dimer and IL-6. Compared to placebo, Xigris-treated patients experienced more rapid declines in D-dimer, PAI-1 levels, thrombin-antithrombin levels, prothrombin F1.2, IL-6, more rapid increases in protein C and antithrombin levels, and normalization of plasminogen. As assessed by infusion duration, the maximum observed pharmacodynamic effect of drotrecogin alfa (activated) on D-dimer levels occurred at the end of 96 hours of infusion for the 24 mcg/kg/hr treatment group.

Human Pharmacokinetics

Xigris and endogenous Activated Protein C are inactivated by endogenous plasma protease inhibitors. Plasma concentrations of endogenous Activated Protein C in healthy subjects and patients with severe sepsis are usually below detection limits.

In patients with severe sepsis, Xigris infusions of 12 mcg/kg/hr to 30 mcg/kg/hr rapidly produce steady state concentrations (C_{ss}) that are proportional to infusion rates. In the Phase 3 trial (*see* **CLINICAL STUDIES**), the median clearance of Xigris was 40 L/hr (interquartile range of 27 to 52 L/hr). The median C_{ss} of 45 ng/mL (interquartile range of 35 to 62 ng/mL) was attained within 2 hours after starting infusion. In the majority of patients, plasma concentrations of Xigris fell below the assay's quantitation limit of 10 ng/mL within 2 hours after stopping infusion. Plasma clearance of Xigris in patients with severe sepsis is approximately 50% higher than that in healthy subjects.

Special Populations

In adult patients with severe sepsis, small differences were detected in the plasma clearance of Xigris with regard to age, gender, hepatic dysfunction, or renal dysfunction. Dose adjustment is not required based on these factors alone or in combination (*see* **PRECAUTIONS**).

End stage renal disease—Patients with end stage renal disease requiring chronic renal replacement therapy were excluded from the Phase 3 study. In patients without sepsis undergoing hemodialysis (n=6), plasma clearance (mean ± SD) of Xigris administered on non-dialysis days was 30 ± 8 L/hr. Plasma clearance of Xigris was 23 ± 4 L/hr in patients without sepsis undergoing peritoneal dialysis (n=5). These clearance rates did not meaningfully differ from those in normal healthy subjects (28 ± 9 L/hr) (n=190).

Pediatrics—Safety and efficacy have not been established in pediatric patients with severe sepsis (*see* **INDICATIONS AND USAGE**), therefore no dosage recommendation can be made. The pharmacokinetics of a dose of 24 mcg/kg/hr of Xigris appear to be similar in pediatric and adult patients with severe sepsis.

Drug-Drug Interactions—Formal drug interactions studies have not been conducted.

CLINICAL STUDIES

Study 1

The efficacy of Xigris was studied in an international, multicenter, randomized, double-blind, placebo-controlled trial (PROWESS) of 1690 patients with severe sepsis.[1] Entry criteria included a systemic inflammatory response presumed due to infection and at least one associated acute organ dysfunction. Acute organ dysfunction was defined as one of the following: cardiovascular dysfunction (shock, hypotension, or the need for vasopressor support despite adequate fluid resuscitation); respiratory dysfunction (relative hypoxemia (PaO_2/FiO_2 ratio <250)); renal dysfunction (oliguria despite adequate fluid resuscitation); thrombocytopenia (platelet count <80,000/mm^3 or 50% decrease from the highest value the previous 3 days); or metabolic acidosis with elevated lactic acid concentrations. Patients received a 96-hour infusion of Xigris at 24 mcg/kg/hr or placebo starting within 48 hours after the onset of the first sepsis induced organ dysfunction. Exclusion criteria encompassed patients at high risk for bleeding (*see* **CONTRAINDICATIONS** *and* **WARNINGS**), patients who were not expected to survive for 28 days due to a pre-existing, non-sepsis related medical condition, HIV positive patients whose most recent CD_4 count was ≤50/mm^3, patients on chronic dialysis, and patients who had undergone bone marrow, lung, liver, pancreas, or small bowel transplantation.

The primary efficacy endpoint was all-cause mortality assessed 28 days after the start of study drug administration. Prospectively defined subsets for mortality analyses included groups defined by APACHE II score[2] (a score designed to assess risk of mortality based on acute physiology and chronic health evaluation, see http://www.sfar.org/scores2/scores2.html), protein C activity, and the number of acute organ dysfunctions at baseline. The APACHE II score was calculated from physiologic and laboratory data obtained within the 24-hour period immediately preceding the start of study drug administration irrespective of the preceding length of stay in the Intensive Care Unit.

The study was terminated after a planned interim analysis due to significantly lower mortality in patients on Xigris than in patients on placebo (210/850, 25% versus 259/840, 31% p=0.005, see Table 1).

Baseline APACHE II score, as measured in PROWESS, was correlated with risk of death; among patients receiving placebo, those with the lowest APACHE II scores had a 12% mortality rate, while those in the 2nd, 3rd, and 4th APACHE quartiles had mortality rates of 26%, 36%, and 49%, respectively. The observed mortality difference between Xigris and placebo was limited to the half of patients with higher risk of death, i.e., APACHE II score ≥25, the 3rd and 4th quartile APACHE II scores (Table 1). The efficacy of Xigris has not been established in patients with lower risk of death, e.g., APACHE II score <25.

[See table 1 below]

Of measures used, the APACHE II score was most effective in classifying patients by risk of death within 28 days and by likelihood of benefit from Xigris, but other important indicators of risk or severity also supported an association between likelihood of Xigris benefit and risk of death. Absolute reductions in mortality of 2%, 5%, 8%, and 11% with Xigris were observed for patients with 1, 2, 3, and 4 or more organ dysfunctions, respectively. Similarly, each of the three major

Table 1: 28-Day All-Cause Mortality for All Patients and for Subgroups Defined by APACHE II Score[a]

	Xigris Total N[b]	N[c] (%)	Placebo Total N[b]	N[c] (%)	Absolute Mortality Difference (%)	Relative Risk (RR)	95% CI for RR
Overall	850	210 (25)	840	259 (31)	-6	0.81	0.70, 0.93
APACHE II quartile (score)							
1st + 2nd (3-24)	436	82 (19)	437	83 (19)	0	0.99	0.75, 1.30
3rd + 4th (25-53)	414	128 (31)	403	176 (44)	-13	0.71	0.59, 0.85

[a] For more information on calculating the APACHE II score, see: http://www.sfar.org/scores2/scores2.html
[b] Total N = Total number of patients in group.
[c] N = Number of deaths in group.

Xigris—Cont.

Preparation and Administration Instructions:

1. Use appropriate aseptic technique during the preparation of Xigris for intravenous administration.
2. Calculate the approximate amount of Xigris needed based upon the patient's actual body weight and duration of this infusion period. The maximum duration of infusion from one preparation step is 12 hours. Multiple infusion periods will be needed to cover the entire 96-hour duration of administration.
   mg of Xigris = (patient weight, kg) X 24 mcg/kg/hr
   X (hours of infusion) ÷ 1000
   Round the actual amount of Xigris to be prepared to the nearest 5 mg increment to avoid discarding reconstituted Xigris.
3. Determine the number of vials of Xigris needed to make up this amount.
4. Reconstitute each vial of Xigris with Sterile Water for Injection, USP. The 5 mg vials must be reconstituted with 2.5 mL; the 20 mg vials with 10 mL. Slowly add the Sterile Water for Injection, USP to the vial and avoid inverting or shaking the vial. Gently swirl each vial until the powder is completely dissolved. The resulting Xigris concentration of the solution is 2 mg/mL.
5. Xigris contains no antibacterial preservatives; the intravenous solution should be prepared immediately after reconstitution of the Xigris in the vial(s). If the vial of reconstituted Xigris is not used immediately, it may be held at controlled room temperature 20° to 25°C (68° to 77°F), but must be used within 3 hours.
6. Inspect the reconstituted Xigris in the vials for particulate matter and discoloration before further dilution. Do not use vials if particulate matter is visible or the solution is discolored.
7. Xigris should be administered via a dedicated intravenous line or a dedicated lumen of a multilumen venous catheter. The ONLY other solutions that can be administered through the same line are 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection, USP; Dextrose Injection, USP; and Dextrose and Sodium Chloride Injection, USP.
8. Avoid exposing Xigris solutions to heat and/or direct sunlight. Studies conducted at the recommended concentrations indicate the Xigris intravenous solution to be compatible with glass infusion bottles, and infusion bags and syringes made of polyvinylchloride, polyethylene, polypropylene, or polyolefin.

Dilution and Administration Instructions for an Intravenous Infusion Pump Using an Infusion Bag:

1. Complete Preparation and Administration steps 1-8, then complete the next 6 steps.
2. The solution of reconstituted Xigris must be further diluted into an infusion bag containing 0.9% Sodium Chloride Injection, USP to a final concentration of between 0.1 mg/mL and 0.2 mg/mL. Bag volumes between 50 mL and 250 mL are typical.
3. Confirm that the intended bag volume will result in an acceptable final concentration.
   Final concentration, mg/mL = (actual Xigris amount, mg)
   ÷ (bag volume, mL)
   If the calculated final concentration is not between 0.1 mg/mL and 0.2 mg/mL select different bag volume and recalculate the final concentration.
4. Slowly withdraw the reconstituted Xigris solution from the vial(s) and add the reconstituted Xigris into the infusion bag of 0.9% Sodium Chloride Injection, USP. When injecting the Xigris into the infusion bag, direct the stream to the side of the bag to minimize the agitation of the solution. Gently invert the infusion bag to obtain a homogeneous solution. Do not transport the infusion bag using mechanical transport systems such as pneumatic-tube systems that may cause vigorous agitation of the solution.
5. Calculate the actual duration of the infusion period for the diluted Xigris.
   Infusion period, hours = (actual Xigris amount, mg)
   X 1000 ÷ (patient weight, kg) ÷ 24 mcg/kg/hr
6. Account for the added volume of reconstituted Xigris (0.5 mL per mg of Xigris used) and the volume of bag saline solution removed (if saline solution is removed prior to adding the reconstituted Xigris).
   Final bag volume, mL = starting bag volume, mL + reconstituted Xigris volume, mL − saline volume removed
   (if any), mL
   Calculate the actual infusion rate of the diluted Xigris.
   Infusion rate, mL/hr = final bag volume, mL ÷ infusion
   period, hours
7. After preparation, the intravenous solution should be used at controlled room temperature 20° to 25°C (68° to 77°F) within 14 hours. If the intravenous solution is not administered immediately, the solution may be stored refrigerated 2° to 8°C (36° to 46°F) for up to 12 hours. If the prepared solution is refrigerated prior to administration, **the maximum time limit for use of the intravenous solution, including preparation, refrigeration, and administration, is 24 hours.**

Dilution and Administration Instructions for a Syringe Pump:

1. Complete Preparation and Administration steps 1-8, then complete the next 7 steps.
2. The solution of reconstituted Xigris must be further diluted with 0.9% Sodium Chloride Injection, USP to a final concentration of between 0.1 mg/mL and 1.0 mg/mL.
3. Confirm that the intended solution volume will result in an acceptable final concentration.
   Final concentration, mg/mL = (actual Xigris amount, mg)
   ÷ (solution volume, mL)
   If the calculated final concentration is not between 0.1 to 1.0 mg/mL select a different volume and recalculate the final concentration.
4. Slowly withdraw the reconstituted Xigris solution from the vial(s) into a syringe that will be used in the syringe pump. Into the same syringe, slowly withdraw 0.9% Sodium Chloride Injection, USP to obtain the desired final volume of diluted Xigris. Gently invert and/or rotate the syringe to obtain a homogenous solution.
5. Calculate the actual duration of the infusion period for the diluted Xigris.
   Infusion period, hours = (actual Xigris amount, mg)
   X 1000 ÷ (patient weight, kg) ÷ 24 mcg/kg/hr
6. Calculate the actual infusion rate of the diluted Xigris.
   Infusion rate, mL/hr = (solution volume, mL) ÷ (infusion
   period, hours)
7. When administering Xigris using a syringe pump at low concentrations (less than approximately 0.2 mg/mL) with low flow rates (less than approximately 5 mL/hr), the infusion set must be primed for approximately 15 minutes at a flow rate of approximately 5 mL/hr.
8. After preparation, the intravenous solution should be used at controlled room temperature 20° to 25°C (68° to 77°F) within 12 hours. **The maximum time limit for use of the intravenous solution, including preparation and administration, is 12 hours.**

HOW SUPPLIED

Xigris is available in 5 mg and 20 mg single-use vials containing sterile, preservative-free, lyophilized drotrecogin alfa (activated).

Vials:

5 mg Vials
  NDC 0002-7559-01
20 mg Vials
  NDC 0002-7561-01

Xigris should be stored in a refrigerator 2° to 8°C (36° to 46°F). Do not freeze. Protect unreconstituted vials of Xigris from light. Retain in carton until time of use. Do not use beyond the expiration date stamped on the vial.

REFERENCES

1. Bernard GR, et al. Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis. *N Engl J Med.* 2001;344:699-709
2. Knaus WA, et al. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13:818-29.

Literature revised June 23, 2005
PV 3427 AMP

Shown in Product Identification Guide, page 320

ZYPREXA® ℞

[*zī-prex-ah*]
Olanzapine Tablets
ZYPREXA® ZYDIS®
Olanzapine Orally Disintegrating Tablets
ZYPREXA® IntraMuscular
Olanzapine for Injection

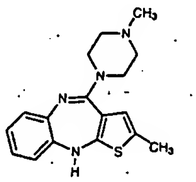
WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (*see* WARNINGS).

DESCRIPTION

ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:

[See chemical structure at top of next column]



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 μmol), 5 mg (16 μmol), 7.5 mg (24 μmol), 10 mg (32 μmol), 15 mg (48 μmol), or 20 mg (64 μmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5.0, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 μmol), 10 mg (32 μmol), 15 mg (48 μmol) or 20 mg (64 μmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only. Each vial provides for the administration of 10 mg (32 μmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ (K_i=4 and 11 nM, respectively), dopamine D_{1-4} (K_i=11-31 nM), muscarinic M_{1-5} (K_i=1.9-25 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β adrenergic receptors (K_i>10 μM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with Bipolar I Disorder is unknown.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Oral Administration

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about one week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (*see* Special Populations).

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1-acid glycoprotein.

Metabolism and Elimination — Following a single oral dose of ^{14}C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

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Intramuscular Administration

ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

Special Populations

Renal Impairment — Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment — Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Age — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (>65 years) than in non-elderly subjects (≤65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity (*see* DOSAGE AND ADMINISTRATION).

Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race — In vivo studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (*see* DOSAGE AND ADMINISTRATION).

For specific information about the pharmacology of lithium or valproate, refer to the CLINICAL PHARMACOLOGY section of the package inserts for these other products.

Clinical Efficacy Data

Schizophrenia

The efficacy of oral olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the two trials, but this trial did not compare these two drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which are embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5.0 ± 2.5 mg/day, 10.0 ± 2.5 mg/day, and 15.0 ± 2.5 mg/day) on a once daily schedule, the two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high dose group over the medium dose group.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

Bipolar Disorder

Monotherapy — The efficacy of oral olanzapine in the treatment of acute manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar disorder who had responded during an initial open-label treatment phase for about two weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤12 and HAM-D 21 to ≤8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to ≥15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Combination Therapy — The efficacy of oral olanzapine with concomitant lithium or valproate in the treatment of acute manic episodes was established in two controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course. The results of the trials follow:

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 μg/mL to 125 μg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 μg/mL to 125 μg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

Agitation Associated with Schizophrenia and Bipolar I Mania

The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated inpatients from two diagnostic groups: schizophrenia and Bipolar I Disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥14 on the five items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least one individual item score ≥4 using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to three injections during the 24 hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), four fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the three highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), one fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for Bipolar I Disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), one fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

INDICATIONS AND USAGE

Schizophrenia

Oral ZYPREXA is indicated for the treatment of schizophrenia.

The efficacy of ZYPREXA was established in short-term (6-week) controlled trials of schizophrenic inpatients (*see* CLINICAL PHARMACOLOGY).

The effectiveness of oral ZYPREXA at maintaining a treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (*see* CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Bipolar Disorder

Acute Monotherapy — Oral ZYPREXA is indicated for the treatment of acute mixed or manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (*see* CLINICAL PHARMACOLOGY).

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA after achieving a responder status for an average duration of two weeks was demonstrated in a controlled trial (*see* Clinical Efficacy Data *under* CLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Continued on next page

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Zyprexa—Cont.

Combination Therapy — The combination of oral ZYPREXA with lithium or valproate is indicated for the short-term treatment of acute manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA in combination with lithium or valproate was established in two placebo-controlled (6-week) trials with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (*see* CLINICAL PHARMACOLOGY).

Agitation Associated with Schizophrenia and Bipolar I Mania

ZYPREXA IntraMuscular is indicated for the treatment of agitation associated with schizophrenia and bipolar I mania. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

The efficacy of ZYPREXA IntraMuscular for the treatment of agitation associated with schizophrenia and bipolar I mania was established in 3 short-term (24 hours) placebo-controlled trials in agitated inpatients with schizophrenia or Bipolar I Disorder (manic or mixed episodes) (*see* CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

ZYPREXA is contraindicated in patients with a known hypersensitivity to the product.

For specific information about the contraindications of lithium or valproate, refer to the CONTRAINDICATIONS section of the package inserts for these other products.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis (*see* BOX WARNING).

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively). Risk factors that may predispose this patient population to increased mortality when treated with olanzapine include age ≥80 years, sedation, concomitant use of benzodiazepines or presence of pulmonary conditions (e.g., pneumonia, with or without aspiration).

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis — Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and Diabetes Mellitus — Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Neuroleptic Malignant Syndrome (NMS) — A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia — A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the WARNINGS section of the package inserts for these other products.

PRECAUTIONS

General

Hemodynamic Effects — Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonistic properties. Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in non-agitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg) (*see* DOSAGE AND ADMINISTRATION). Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs.

For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD (*see* DOSAGE AND ADMINISTRATION). A more gradual titration to the target dose should be considered if hypotension occurs.

For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression (*see* Drug Interactions). Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended. If use of intramuscular olanzapine in combination with parenteral benzodiazepines is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Seizures — During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hyperprolactinemia — As with other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels, and a modest elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Transaminase Elevations — In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. In two of these patients, liver enzymes decreased toward normal despite continued treatment and in two others, enzymes decreased upon discontinuation of olanzapine. In the remaining two patients, one, seropositive for hepatitis C, had persistent enzyme elevation for four months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

Among 2500 patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Laboratory Tests).

Potential for Cognitive and Motor Impairment — Somnolence was a commonly reported adverse event associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse event was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Body Temperature Regulation — Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to

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Dysphagia — Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide — The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness — Clinical experience with olanzapine in patients with certain concomitant systemic illnesses (*see* Renal Impairment and Hepatic Impairment *under* CLINICAL PHARMACOLOGY, Special Populations) is limited.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse events were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%). As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (*see* BOX WARNING *and* WARNINGS).

Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients (*see* Hemodynamic Effects).

For specific information about the precautions of lithium or valproate, refer to the PRECAUTIONS section of the package inserts for these other products.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe olanzapine:

Orthostatic Hypotension — Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol (*see* Drug Interactions).

Interference with Cognitive and Motor Performance — Because olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Pregnancy — Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with olanzapine.

Nursing — Patients should be advised not to breast-feed an infant if they are taking olanzapine.

Concomitant Medication — Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol — Patients should be advised to avoid alcohol while taking olanzapine.

Heat Exposure and Dehydration — Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Phenylketonurics — ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively).

Laboratory Tests

Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Transaminase Elevations).

Drug Interactions

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents.

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Olanzapine — Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

Charcoal — The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Carbamazepine — Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Ethanol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics.

Fluoxetine — Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

Fluvoxamine — Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics.

Effect of Olanzapine on Other Drugs — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium.

Valproate — Studies in vitro using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. In vivo administration of olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam, ethanol, or biperiden. However, the co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

Lorazepam — Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone (*see* Hemodynamic Effects).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily oral dose on a mg/m^2 basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a mg/m^2 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m^2 basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a mg/m^2 basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown (*see* Hyperprolactinemia *under* PRECAUTIONS, General).

Mutagenesis — No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility — In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily oral dose on a mg/m^2 basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m^2 basis); therefore olanzapine may produce a delay in ovulation.

Pregnancy

Pregnancy Category C — In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m^2 basis). In an oral rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the maximum recommended human daily oral dose on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

Nursing Mothers

Olanzapine was excreted in milk of treated rats during lactation. It is not known if olanzapine is excreted in human milk. It is recommended that women receiving olanzapine should not breast-feed.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient (*see* BOX WARNING, WARNINGS, PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for olanzapine consisting of 8661 patients with approximately 4165 patient-years of exposure to oral olanzapine

Continued on next page

This product information was prepared in June 2005. Current information on products of Eli Lilly and Company may be obtained by calling 1-800-545-5979.

Zyprexa—Cont.

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY RATING SCALES INCIDENCE IN A FIXED DOSE, PLACEBO-CONTROLLED CLINICAL TRIAL OF INTRAMUSCULAR OLANZAPINE FOR INJECTION IN AGITATED PATIENTS WITH SCHIZOPHRENIA*

	Percentage of Patients Reporting Event				
	Placebo	Olanzapine IM 2.5 mg	Olanzapine IM 5 mg	Olanzapine IM 7.5 mg	Olanzapine IM 10 mg
Parkinsonism[1]	0	0	0	0	3
Akathisia[2]	0	0	5	0	0

* No statistically significant differences.

[1] Percentage of patients with a Simpson-Angus total score >3.

[2] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY ADVERSE EVENTS INCIDENCE IN A FIXED DOSE, PLACEBO-CONTROLLED CLINICAL TRIAL OF INTRAMUSCULAR OLANZAPINE FOR INJECTION IN AGITATED PATIENTS WITH SCHIZOPHRENIA*

	Percentage of Patients Reporting Event				
	Placebo (N=45)	Olanzapine IM 2.5 mg (N=48)	Olanzapine IM 5 mg (N=45)	Olanzapine IM 7.5 mg (N=46)	Olanzapine IM 10 mg (N=46)
Dystonic events[1]	0	0	0	0	0
Parkinsonism events[2]	0	4	2	0	0
Akathisia events[3]	0	2	0	0	0
Dyskinetic events[4]	0	0	0	0	0
Residual events[5]	0	0	0	0	0
Any extrapyramidal event	0	4	2	0	0

* No statistically significant differences.

[1] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[2] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[3] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[4] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[5] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

	Percentage of Patients Reporting Event			
Adverse Event	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Asthenia	15	8	9	20
Dry mouth	4	3	5	13
Nausea	9	0	2	9
Somnolence	16	20	30	39
Tremor	3	0	5	7

sociated with increases in serum prolactin (*see* PRECAUTIONS), with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models (*see* ANIMAL TOXICOLOGY), careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

In clinical trials among olanzapine-treated patients with random triglyceride levels of <150 mg/dL at baseline (N=485), 0.6% of patients experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=962) had a mean increase of 27 mg/dL in triglycerides from a mean baseline value of 185 mg/dL.

In placebo-controlled trials, olanzapine-treated patients with random cholesterol levels of <200 mg/dL at baseline (N=1439) experienced cholesterol levels of ≥240 mg/dL anytime during the trials significantly more often than placebo-treated patients (N=836) (8.1% vs 3.8%, respectively). In these same trials, olanzapine-treated patients (N=2528) had a mean increase of 1 mg/dL in cholesterol from a mean baseline value of 203 mg/dL, which was significantly different compared to placebo-treated patients (N=1420) with a mean decrease of 4 mg/dL from a mean baseline value of 203 mg/dL.

ECG Changes — Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine use was associated with a mean increase in heart rate of 2.4 beats per minute compared to no change among placebo patients. This slight tendency to tachycardia may be related to olanzapine's potential for inducing orthostatic changes (*see* PRECAUTIONS).

Other Adverse Events Observed During the Clinical Trial Evaluation of Olanzapine

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) in clinical trials (8661 patients, 4165 patient-years of exposure). This listing may not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole — *Frequent:* dental pain and flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, and suicide attempt; *Rare:* chills and fever, hangover effect, and sudden death.

Cardiovascular System — *Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, and ventricular extrasystoles; *Rare:* arteritis, heart failure, and pulmonary embolus.

Digestive System — *Frequent:* flatulence, increased salivation, and thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, and tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, and tongue discoloration.

Endocrine System — *Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis and goiter.

Hemic and Lymphatic System — *Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, and thrombocytopenia; *Rare:* normocytic anemia and thrombocythemia.

Metabolic and Nutritional Disorders — *Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, and upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, and water intoxication.

Musculoskeletal System — *Frequent:* joint stiffness and twitching; *Infrequent:* arthritis, arthrosis, leg cramps, and myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, and rheumatoid arthritis.

Nervous System — *Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, and schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, and withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, and tobacco misuse.

Respiratory System — *Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, and voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, and stridor.

Skin and Appendages — *Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, and vesiculobullous rash; *Rare:* hirsutism and pustular rash.

Special Senses — *Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, and tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, and pigment deposits lens.

Urogenital System — *Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation*, amenorrhea*, breast pain, cystitis, decreased menstruation*, dysuria, female lactation*, glycosuria, gynecomastia, hematuria, impotence*, increased menstruation*, menorrhagia*, metrorrhagia*, polyuria, premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged*; and vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, and oliguria.

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* Adjusted for gender.

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with intramuscular olanzapine for injection (at one or more doses ≥2.5 mg/injection) in clinical trials (722 patients). This listing may not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients.

Body as a Whole — *Frequent:* injection site pain; *Infrequent:* abdominal pain and fever.

Cardiovascular System — *Infrequent:* AV block, heart block, and syncope.

Digestive System — *Infrequent:* diarrhea and nausea.

Hemic and Lymphatic System — *Infrequent:* anemia.

Metabolic and Nutritional Disorders — *Infrequent:* creatine phosphokinase increased, dehydration, and hyperkalemia.

Musculoskeletal System — *Infrequent:* twitching.

Nervous System — *Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, and emotional lability.

Skin and Appendages — *Infrequent:* sweating.

Postintroduction Reports

Adverse events reported since market introduction that were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been rarely reported.

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DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Olanzapine is not a controlled substance.

Physical and Psychological Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dose on a mg/m^2 basis.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and one patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In one case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

Overdosage Management

The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Dose — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant Illness and Drug Interactions *under* PRECAUTIONS). When indicated, dose escalation should be performed with caution in these patients.

	TABLET STRENGTH					
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Tablet No.	4112	4115	4116	4117	4415	4420
Identification	LILLY 4112	LILLY 4115	LILLY 4116	LILLY 4117	LILLY 4415	LILLY 4420
NDC Codes:						
Bottles 60	NDC 0002-4112-60	NDC 0002-4115-60	NDC 0002-4116-60	NDC 0002-4117-60	NDC 0002-4415-60	NDC 0002-4420-60
Blisters - ID* 100	NDC 0002-4112-33	NDC 0002-4115-33	NDC 0002-4116-33	NDC 0002-4117-33	NDC 0002-4415-33	NDC 0002-4420-33
Bottles 1000	NDC 0002-4112-04	NDC 0002-4115-04	NDC 0002-4116-04	NDC 0002-4117-04	NDC 0002-4415-04	NDC 0002-4420-04

*Identi-Dose® (unit dose medication, Lilly).

ZYPREXA ZYDIS Tablets*	TABLET STRENGTH			
	5 mg	10 mg	15 mg	20 mg
Tablet No.	4453	4454	4455	4456
Debossed	5	10	15	20
NDC Codes:				
Dose Pack 30 (Child-Resistant).	NDC 0002-4453-85	NDC 0002-4454-85	NDC 0002-4455-85	NDC 0002-4456-85

ZYPREXA is a registered trademark of Eli Lilly and Company.

ZYDIS is a registered trademark of Cardinal Health, Inc. or one of its subsidiaries.

*ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Cardinal Health, United Kingdom, SN5 8RU.

Maintenance Treatment — While there is no body of evidence available to answer the question of how long the patient treated with olanzapine should remain on it, the effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (*see* CLINICAL PHARMACOLOGY). Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

Bipolar Disorder

Usual Monotherapy Dose — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of two weeks, was demonstrated in a controlled trial (*see* Clinical Efficacy Data *under* CLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Bipolar Mania Usual Dose in Combination with Lithium or Valproate — When administered in combination with lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Short-term (6 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations — *See* Dosing in Special Populations *under* DOSAGE AND ADMINISTRATION, Schizophrenia.

Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)

After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

Agitation Associated with Schizophrenia and Bipolar I Mania

Usual Dose for Agitated Patients with Schizophrenia or Bipolar Mania — The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant (*see* CLINICAL PHARMACOLOGY). If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., three doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension (*see* PRECAUTIONS, Hemodynamic Effects). Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate (*see* Schizophrenia or Bipolar Disorder *under* DOSAGE AND ADMINISTRATION).

Intramuscular Dosing in Special Populations — A dose of 5 mg per injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg per injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant Illness and Drug Interactions *under* PRECAUTIONS).

Administration of ZYPREXA IntraMuscular

ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for preparation of ZYPREXA IntraMuscular with Sterile Water for Injection

Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. **Discard any unused portion.**

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

Dose, mg Olanzapine	Volume of Injection, mL
10.0	Withdraw total contents of vial
7.5	1.5
5.0	1.0
2.5	0.5

Physical Incompatibility Information

ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection. ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

HOW SUPPLIED

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

[See first table above]

Continued on next page

This product information was prepared in June 2005. Current information on products of Eli Lilly and Company may be obtained by calling 1-800-545-5979.

Zyprexa—Cont.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

[See second table at top of previous page]

ZYPREXA IntraMuscular is available in:

NDC 0002-7597-01 (No. VL7597) – 10 mg vial (1s)

Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP] for up to 1 hour if necessary. **Discard any unused portion of reconstituted ZYPREXA IntraMuscular.** The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect ZYPREXA IntraMuscular from light, do not freeze.

ANIMAL TOXICOLOGY

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on a mg/m^2 basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a mg/m^2 basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a mg/m^2 basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m^2 basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

Literature revised April 14, 2005

www.ZYPREXA.com

PV 3518 AMP

Shown in Product Identification Guide, page 320

Lilly ICOS LLC

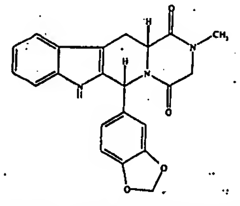
c/o ELI LILLY AND COMPANY
LILLY CORPORATE CENTER
INDIANAPOLIS, IN 46285

Direct Inquiries to:
Lilly ICOS LLC
c/o Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000
www.cialis.com
For Medical Information Contact:
Lilly ICOS LLC
1-877-Cialis-1

CIALIS® ℞
[see-AL-iss]
(tadalafil)
tablets

DESCRIPTION

CIALIS® (tadalafil), an oral treatment for erectile dysfunction, is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. The structural formula is:



The chemical designation is pyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

CIALIS is available as film-coated, almond-shaped tablets for oral administration. Each tablet contains 5, 10, or 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

CLINICAL PHARMACOLOGY

Mechanism of Action

Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by tadalafil has no effect in the absence of sexual stimulation.

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas.

In vitro studies have shown that the effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. These studies have shown that tadalafil is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle, and other organs. Tadalafil is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. Additionally, tadalafil is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10 and 14-fold more potent for PDE5 than for PDE11A1, an enzyme found in human skeletal muscle. Tadalafil inhibits human recombinant PDE11A1 activity at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined.

Pharmacokinetics

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Steady-state plasma concentrations are attained within 5 days of once-daily dosing, and exposure is approximately 1.6-fold greater than after a single dose. Tadalafil is eliminated predominantly by hepatic metabolism, mainly by cytochrome P450 3A4 (CYP3A4). The concomitant use of potent CYP3A4 inhibitors such as ritonavir or ketoconazole resulted in significant increases in tadalafil AUC values (*see* **PRECAUTIONS** *and* **DOSAGE AND ADMINISTRATION**). Mean tadalafil concentrations measured after the administration of a single oral dose of 20 mg to healthy male subjects are depicted in Figure 1.

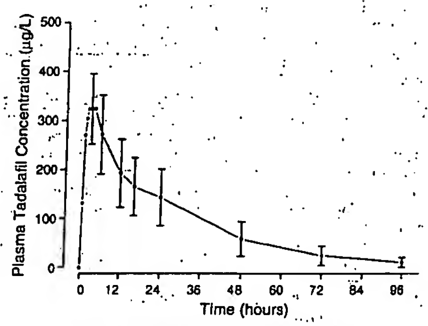


Figure 1: Plasma tadalafil concentrations (mean ± SD) following a single 20-mg tadalafil dose

Absorption—After single oral-dose administration, the maximum observed plasma concentration (C_{max}) of tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food; thus CIALIS may be taken with or without food.

Distribution—The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.

Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism—Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. *In vitro* data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Elimination—The mean oral clearance for tadalafil is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Pharmacokinetics in Special Populations

Geriatric—Healthy male elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 years of age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered (*see* **Geriatric Use** *under* **PRECAUTIONS**).

Pediatric—Tadalafil has not been evaluated in individuals less than 18 years old.

Hepatic Impairment—In clinical pharmacology studies, tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of tadalafil in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C). Therefore, for patients with mild or moderate hepatic impairment, the maximum dose should not exceed 10 mg, and use in patients with severe hepatic impairment is not recommended (*see* **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency—In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.1-fold increase in AUC following single-dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24 and 30 hours post-dose) contributed negligibly to tadalafil or metabolite elimination. In a clinical pharmacology study (N=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in male patients with moderate renal impairment. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on hemodialysis taking 10- or 20-mg tadalafil, there were no reported cases of back pain. The dose of tadalafil should be limited to 5 mg not more than once daily in patients with severe renal insufficiency or end-stage renal disease. A starting dose of 5 mg not more than once daily is recommended for patients with moderate renal insufficiency; the maximum recommended dose is 10 mg not more than once in every 48 hours. No dose adjustment is required in patients with mild renal insufficiency (*see* **DOSAGE AND ADMINISTRATION**).

Patients with Diabetes Mellitus—In male patients with diabetes mellitus after a 10 mg tadalafil dose, exposure (AUC) was reduced approximately 19% and C_{max} was 5% lower than that observed in healthy subjects. No dose adjustment is warranted.

Pharmacodynamics

Effects on Blood Pressure—Tadalafil 20 mg administered to healthy male subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8 mm Hg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mm Hg, respectively). In addition, there was no significant effect on heart rate.

Effects on Blood Pressure when CIALIS is Administered with Nitrates—In clinical pharmacology studies, tadalafil (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of CIALIS in patients taking any form of nitrates is contraindicated (*see* **CONTRAINDICATIONS**).

A study was conducted to assess the degree of interaction between nitroglycerin and tadalafil, should nitroglycerin be required in an emergency situation after tadalafil was taken. This was a double-blind, placebo-controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) and receiving daily doses of tadalafil 20 mg or matching placebo for 7 days. Subjects were administered a single dose of 0.4 mg sublingual nitroglycerin (NTG) at pre-specified timepoints, following their last dose of tadalafil (2, 4, 8, 24, 48, 72, and 96 hours after tadalafil). The objective of the study was to determine when, after tadalafil dosing, no apparent blood pressure interaction was observed. In this study, a significant interaction between tadalafil and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between tadalafil and NTG was not observed, although a few more tadalafil subjects compared to placebo experienced greater blood-pressure lowering at this timepoint. After 48 hours, the interaction was not detectable (see Figure 2).

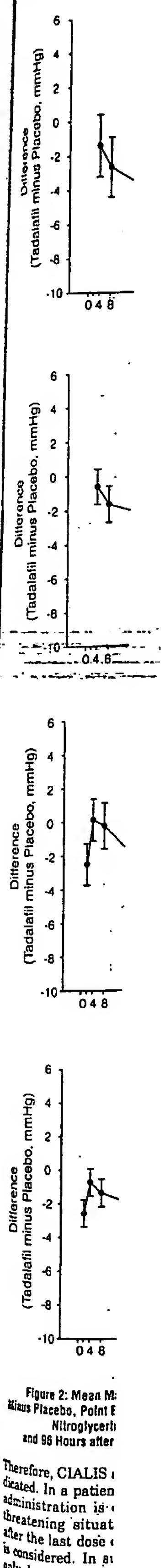


Figure 2: Mean M
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CONTRAINDICA
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Table 11. CADUET Packaging Configurations

		CADUET		
Package Configuration	Tablet Strength (amlodipine besylate/ atorvastatin calcium) mg	NDC #	Engraving	Tablet Color
Bottle of 30	2.5/10	0069-2960-30	CDT 251	White
Bottle of 30	2.5/20	0069-2970-30	CDT 252	White
Bottle of 30	2.5/40	0069-2980-30	CDT 254	White
Bottle of 30	5/10	0069-2150-30	CDT 051	White
Bottle of 30	5/20	0069-2170-30	CDT 052	White
Bottle of 30	5/40	0069-2190-30	CDT 054	White
Bottle of 30	5/80	0069-2260-30	CDT 058	White
Bottle of 30	10/10	0069-2160-30	CDT 101	Blue
Bottle of 30	10/20	0069-2180-30	CDT 102	Blue
Bottle of 30	10/40	0069-2250-30	CDT 104	Blue
Bottle of 30	10/80	0069-2270-30	CDT 108	Blue

Caduet—Cont.

Dosage In Patients With Renal Insufficiency

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

CADUET

CADUET may be substituted for its individually titrated components. Patients may be given the equivalent dose of CADUET or a dose of CADUET with increased amounts of amlodipine, atorvastatin or both for additional antianginal effects, blood pressure lowering, or lipid lowering effect.

CADUET may be used to provide additional therapy for patients already on one of its components. As initial therapy for one indication and continuation of treatment of the other, the recommended starting dose of CADUET should be selected based on the continuation of the component being used and the recommended starting dose for the added monotherapy.

CADUET may be used to initiate treatment in patients with hyperlipidemia and either hypertension or angina. The recommended starting dose of CADUET should be based on the appropriate combination of recommendations for the monotherapies. The maximum dose of the amlodipine component of CADUET is 10 mg once daily. The maximum dose of the atorvastatin component of CADUET is 80 mg once daily.

See above for detailed information related to the dosing and administration of amlodipine and atorvastatin.

HOW SUPPLIED

CADUET® tablets contain amlodipine besylate and atorvastatin calcium equivalent to amlodipine and atorvastatin in the dose strengths described below.

CADUET tablets are differentiated by tablet color/size and are engraved with "Pfizer" on one side and a unique number on the other side. CADUET tablets are supplied for oral administration in the following strengths and package configurations:

[See table 11 above]

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Rx only

Manufactured by:
Pfizer Ireland Pharmaceuticals
Dublin, Ireland
Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

LAB-0276-3.0 **Revised October 2004**

Shown in Product Identification Guide, page 329

GEODON® ℞

[gē-ō-dōn]
(ziprasidone HCl)
Capsules

GEODON®

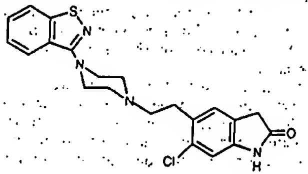
(ziprasidone mesylate)
for Injection
FOR IM USE ONLY

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Geodon (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

GEODON® is available as GEODON Capsules (ziprasidone hydrochloride) for oral administration and as GEODON for Injection (ziprasidone mesylate) for intramuscular injection. Ziprasidone is a psychotropic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one. The empirical formula of $C_{21}H_{21}ClN_4OS$ (free base of ziprasidone) represents the following structural formula:



GEODON Capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$ and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powder.

GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. GEODON Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

GEODON for Injection contains a lyophilized form of ziprasidone mesylate trihydrate. Chemically, ziprasidone mesylate trihydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, methanesulfonate, trihydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot CH_3SO_3H \cdot 3H_2O$ and its molecular weight is 563.09.

GEODON for Injection is available in a single dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions - see **Preparation for Administration**) for intramuscular administration. Each mL of ziprasidone mesylate for injection (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$, $5HT_{1D}$, and α_1-adrenergic receptors (K_i s of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively), and moderate affinity for the histamine H_1 receptor (K_i=47 nM). Ziprasidone functioned as an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and as an agonist at the $5HT_{1A}$ receptor. Ziprasidone inhibited synaptic reuptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC_{50} >1 μM).

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. As with other drugs having efficacy in bipolar disorder, the mechanism of action of ziprasidone in bipolar disorder is unknown. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone. Ziprasidone's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Ziprasidone's antagonism of α_1-adrenergic receptors may explain the orthostatic hypotension observed with this drug.

Oral Pharmacokinetics

Ziprasidone's activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of ziprasidone are dose-proportional within the proposed clinical dose range, and ziprasidone accumulation is predictable with multiple dosing. Elimination of ziprasidone is mainly via hepatic metabolism with a mean terminal half-life of about 7 hours within the proposed clinical dose range. Steady-state concentrations are achieved within one to three days of dosing. The mean apparent systemic clearance is 7.5 mL/min/kg. Ziprasidone is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Ziprasidone is well absorbed after oral administration, reaching peak plasma concentrations in 6 to 8 hours. The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%. The absorption of ziprasidone is increased up to two-fold in the presence of food.

Distribution: Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to plasma proteins, binding primarily to albumin and α_1-acid glycoprotein. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is minimal.

Metabolism and Elimination: Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole (BITP) sulphoxide, BITP-sulphone, ziprasidone sulphoxide, and S-methyl-dihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum. *In vitro* studies using human liver subcellular fractions indicate that S-methyl-dihydroziprasidone is generated in two steps. The data indicate that the reduction reaction is mediated by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on *in vivo* abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

Intramuscular Pharmacokinetics

Systemic Bioavailability: The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 60 minutes post-dose or earlier and the mean half-life ($T_{½}$) ranges from two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Metabolism and Elimination: Although the metabolism and elimination of IM ziprasidone have not been systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

Special Populations

Age and Gender Effects—In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between men and women or between elderly (>65 years) and young (18 to 45 years) subjects. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant age or gender-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for age or gender are, therefore, not recommended.

Ziprasidone intramuscular has not been systematically evaluated in elderly patients (65 years and over).

Race—No specific pharmacokinetic study was conducted to investigate the effects of race. Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for race are, therefore, not recommended.

Smoking—Based on *in vitro* studies utilizing human liver enzymes, ziprasidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of ziprasidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any significant pharmacokinetic differences between smokers and nonsmokers.

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Renal Impairment—Because ziprasidone is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. The pharmacokinetics of ziprasidone following 8 days of 20 mg BID dosing were similar among subjects with varying degrees of renal impairment (n=27), and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required. Ziprasidone is not removed by hemodialysis.

Hepatic Impairment—As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone; a multiple-dose study at 20 mg BID for 5 days in subjects (n=13) with clinically significant (Childs-Pugh Class A and B) cirrhosis revealed an increase in AUC_{0-12} of 13% and 34% in Childs-Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

Intramuscular ziprasidone has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function.

Drug-Drug Interactions

An *in vitro* enzyme inhibition study utilizing human liver microsomes showed that ziprasidone had little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and thus would not likely interfere with the metabolism of drugs primarily metabolized by these enzymes. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of dextromethorphan, estrogen, progesterone, or lithium (see **Drug Interactions** under **PRECAUTIONS**).

In vivo studies have revealed an approximately 35% decrease in ziprasidone AUC by concomitantly administered carbamazepine, an approximately 35-40% increase in ziprasidone AUC by concomitantly administered ketoconazole, but no effect on ziprasidone's pharmacokinetics by cimetidine or antacid (see **Drug Interactions** under **PRECAUTIONS**).

Clinical Trials

Schizophrenia

The efficacy of oral ziprasidone in the treatment of schizophrenia was evaluated in 5 placebo-controlled studies, 4 short-term (4- and 6-week) trials and one long-term (52-week) trial. All trials were in inpatients, most of whom met DSM III-R criteria for schizophrenia. Each study included 2 to 3 fixed doses of ziprasidone as well as placebo. Four of the 5 trials were able to distinguish ziprasidone from placebo; one short-term study did not. Although a single fixed-dose haloperidol arm was included as a comparative treatment in one of the three short-term trials, this single study was inadequate to provide a reliable and valid comparison of ziprasidone and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies. The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) are both multi-item inventories of general psychopathology usually used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second widely used assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS) was employed for assessing negative symptoms in one trial.

The results of the oral ziprasidone trials in schizophrenia follow:

(1) In a 4-week, placebo-controlled trial (n=139) comparing 2 fixed doses of ziprasidone (20 and 60 mg BID) with placebo, only the 60 mg BID dose was superior to placebo on the BPRS total score and the CGI severity score. This higher dose group was not superior to placebo on the BPRS psychosis cluster or on the SANS.

(2) In a 6-week, placebo-controlled trial (n=302) comparing 2 fixed doses of ziprasidone (40 and 80 mg BID) with placebo, both dose groups were superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score and the PANSS total and negative subscale scores. Although 80 mg BID had a numerically greater effect than 40 mg BID, the difference was not statistically significant.

(3) In a 6-week, placebo-controlled trial (n=419) comparing 3 fixed doses of ziprasidone (20, 60, and 100 mg BID) with placebo, all three dose groups were superior to placebo on the PANSS total score, the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. Only the 100 mg BID dose group was superior to placebo on the PANSS negative subscale score. There was no clear evidence for a dose-response relationship within the 20 mg BID to 100 mg BID dose range.

(4) In a 4-week, placebo-controlled trial (n=200) comparing 3 fixed doses of ziprasidone (5, 20, and 40 mg BID), none of the dose groups was statistically superior to placebo on any outcome of interest.

(5) A study was conducted in chronic, symptomatically stable schizophrenic inpatients (n=294) randomized to 3 fixed doses of ziprasidone (20, 40, or 80 mg BID) or placebo and followed for 52 weeks. Patients were observed for "impending psychotic relapse," defined as CGI-improvement score of ≥6 (much worse or very much worse) and/or scores ≥6 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days. Ziprasidone was significantly superior to placebo in both time to relapse and rate of relapse, with no significant difference between the different dose groups.

There were insufficient data to examine population subsets based on age and race. Examination of population subsets based on gender did not reveal any differential responsiveness.

Bipolar Mania

The efficacy of ziprasidone in acute mania was established in 2 placebo-controlled, double-blind, 3-week studies in patients meeting DSM-IV criteria for Bipolar I Disorder with an acute manic or mixed episode with or without psychotic features.

Primary rating instruments used for assessing manic symptoms in these trials were: (1) the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-CB) with items grouped as the Manic Syndrome subscale (elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity), the Behavior and Ideation subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment) and impaired insight; and (2) the Clinical Global Impression – Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response.

The results of the oral ziprasidone trials in bipolar mania follow:

(1) In a 3-week placebo-controlled trial (n=210), the dose of ziprasidone was 40 mg BID on Day 1 and 80 mg BID on Day 2. Titration within the range of 40-80 mg BID (in 20 mg BID increments) was permitted for the duration of the study. Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 132 mg.

(2) In a second 3-week placebo-controlled trial (n=205), the dose of ziprasidone was 40 mg BID on Day 1. Titration within the range of 40-80 mg BID (in 20 mg BID increments) was permitted for the duration of study (beginning on Day 2). Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 112 mg.

Acute Agitation in Schizophrenic Patients

The efficacy of intramuscular ziprasidone in the management of agitated schizophrenic patients was established in two short-term, double-blind trials of schizophrenic subjects who were considered by the investigators to be "acutely agitated" and in need of IM antipsychotic medication. In addition, patients were required to have a score of 3 or more on at least 3 of the following items of the PANSS: anxiety, tension, hostility and excitement. Efficacy was evaluated by analysis of the area under the curve (AUC) of the Behavioural Activity Rating Scale (BARS) and Clinical Global Impression (CGI) severity rating. The BARS is a seven point scale with scores ranging from 1 (difficult or unable to rouse) to 7 (violent, requires restraint). Patients' scores on the BARS at baseline were mostly 5 (signs of overt activity [physical or verbal], calms down with instructions) and as determined by investigators, exhibited a degree of agitation that warranted intramuscular therapy. There were few patients with a rating higher than 5 on the BARS, as the most severely agitated patients were generally unable to provide informed consent for participation in pre-marketing clinical trials.

Both studies compared higher doses of ziprasidone intramuscular with a 2 mg control dose. In one study, the higher dose was 20 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 4 hours. In the other study, the higher dose was 10 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 2 hours.

The results of the intramuscular ziprasidone trials follow:

(1) In a one-day, double-blind, randomized trial (n=79) involving doses of ziprasidone intramuscular of 20 mg or 2 mg, up to QID, ziprasidone intramuscular 20 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 4 hours, and by CGI severity at 4 hours and study endpoint.

(2) In another one-day, double-blind, randomized trial (n=117) involving doses of ziprasidone intramuscular of 10 mg or 2 mg, up to QID, ziprasidone intramuscular 10 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 2 hours, but not by CGI severity.

INDICATIONS AND USAGE

Schizophrenia

Ziprasidone is indicated for the treatment of schizophrenia. When deciding among the alternative treatments available for this condition, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs (see **WARNINGS**). Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether ziprasidone will cause torsade de pointes or increase the rate of sudden death is not yet known (see **WARNINGS**).

The efficacy of oral ziprasidone was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY**).

In a placebo-controlled trial involving the follow-up for up to 52 weeks of stable schizophrenic inpatients, GEODON was demonstrated to delay the time to and rate of relapse. The physician who elects to use GEODON for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Bipolar Mania

Ziprasidone is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. A mixed episode is characterized by the criteria for a manic episode in conjunction with those for a major depressive episode (depressed mood, loss of interest or pleasure in nearly all activities).

The efficacy of ziprasidone in acute mania was established in 2 placebo-controlled, double-blind, 3-week studies in patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see **CLINICAL PHARMACOLOGY**).

The effectiveness of ziprasidone for longer-term use and for prophylactic use in mania has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use ziprasidone for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Acute Agitation in Schizophrenic Patients

Ziprasidone intramuscular is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Schizophrenic patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation. The efficacy of intramuscular ziprasidone for acute agitation in schizophrenia was established in single-day controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY**). Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

CONTRAINDICATIONS

QT Prolongation

Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**).

Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with dofetilide, sotalol, quinidine, other Class Ia and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus. Ziprasidone is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**).

Hypersensitivity

Ziprasidone is contraindicated in individuals with a known hypersensitivity to the product.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Geodon (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).

QT Prolongation and Risk of Sudden Death

Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QTc interval (see CONTRAINDICATIONS, and see Drug Interactions under PRECAUTIONS). Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS).

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained

Continued on next page

Geodon—Cont.

at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was co-administered with an inhibitor of the CYP4503A4 metabolism of the drug.

In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine.

In the second phase of the study, the effect of ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg BID).

In placebo-controlled trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials with oral ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. One patient had a history of prolonged QTc and a screening measurement of 489 msec; QTc was 503 msec during ziprasidone treatment. The other patient had a QTc of 391 msec at the end of treatment with ziprasidone and upon switching to thioridazine experienced QTc measurements of 518 and 593 msec.

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of ziprasidone at recommended doses in premarketing studies, experience is too limited to rule out an increased risk (see ADVERSE REACTIONS; Other Events Observed During Post-marketing Use).

A study evaluating the QT/QTc prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QTc from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patients had a QTc interval exceeding 500 msec.

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, ziprasidone's larger prolongation of QTc length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products (see INDICATIONS AND USAGE).

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistently prolonged QTc intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

For patients taking ziprasidone who experience symptoms that could indicate the occurrence of torsade de pointes, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, e.g., Holter monitoring may be useful.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ziprasidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. However, some patients may require treatment with ziprasidone despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON. Although fewer patients have been treated with GEODON, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies, which did not include GEODON, suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because GEODON was not marketed at the time these studies were performed, it is not known if GEODON is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Rash—In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these events were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued.

Orthostatic Hypotension—Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with ziprasidone.

Ziprasidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures—During clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Dysphagia—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also Boxed WARNING, WARNINGS: **Increased Mortality in Elderly Patients with Dementia-Related Psychosis**).

Hyperprolactinemia—As with other drugs that antagonize dopamine D_2 receptors, ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment—Somnolence was a commonly reported adverse event in patients treated with ziprasidone. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that ziprasidone therapy does not affect them adversely.

Priapism—One case of priapism was reported in the premarketing database. While the relationship of the event to

ziprasidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that ziprasidone may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation—Although not reported with ziprasidone in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ziprasidone for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Suicide—The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness—Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses (see **Renal Impairment** and **Hepatic Impairment** under **CLINICAL PHARMACOLOGY, Special Populations**) is limited.

Ziprasidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QTc prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients (see **QTc Prolongation** under **WARNINGS** and **Orthostatic Hypotension** under **PRECAUTIONS**).

Information for Patients

Please refer to the patient package insert. To assure safe and effective use of GEODON, the information and instructions provided in the patient information should be discussed with patients.

Laboratory Tests

Patients being considered for ziprasidone treatment that are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before proceeding with treatment. Patients who are started on diuretics during ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec (see **WARNINGS**).

Drug Interactions

Drug-drug interactions can be pharmacodynamic (combined pharmacologic effects) or pharmacokinetic (alteration of plasma levels). The risks of using ziprasidone in combination with other drugs have been evaluated as described below. All interactions studies have been conducted with oral ziprasidone. Based upon the pharmacodynamic and pharmacokinetic profile of ziprasidone, possible interactions could be anticipated:

Pharmacodynamic Interactions

(1) Ziprasidone should not be used with any drug that prolongs the QT interval (see **CONTRAINDICATIONS**).
(2) Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs.
(3) Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents.
(4) Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

Pharmacokinetic Interactions

The Effect of Other Drugs on Ziprasidone

Carbamazepine—Carbamazepine is an inducer of CYP3A4; administration of 200 mg BID for 21 days resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.

Ketoconazole—Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg QD for 5 days, increased the AUC and Cmax of ziprasidone by about 35-40%. Other inhibitors of CYP3A4 would be expected to have similar effects.

Cimetidine—Cimetidine at a dose of 800 mg QD for 2 days did not affect ziprasidone pharmacokinetics.

Antacid—The coadministration of 30 mL of Maalox® with ziprasidone did not affect the pharmacokinetics of ziprasidone.

In addition, population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam.

Effect of Ziprasidone on Other Drugs

In vitro studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Lithium—Ziprasidone at a dose of 40 mg BID administered concomitantly with lithium at a dose of 450 mg BID for 7 days did not affect the steady-state level or renal clearance of lithium.

Oral Contraceptives—Ziprasidone at a dose of 20 mg BID did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg).

Dextromethorphan—Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis—Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months in the diet at doses of 2, 6, or 12 mg/kg/day to rats, and 50, 100, or 200 mg/kg/day to mice (0.1 to 0.6 and 1 to 5 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 basis, respectively). In the rat study, there was no evidence of an increased incidence of tumors compared to controls. In male mice, there was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested (50 to 200 mg/kg/day or 1 to 5 times the MRHD on a mg/m^2 basis). Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice at 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD on a mg/m^2 basis). Ziprasidone had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see **Hyperprolactinemia** under **PRECAUTIONS, General**).

Mutagenesis—Ziprasidone was tested in the Ames bacterial mutation assay, the *in vitro* mammalian cell gene mutation mouse lymphoma assay, the *in vitro* chromosomal aberration assay in human lymphocytes, and the *in vivo* chromosomal aberration assay in mouse bone marrow. There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes.

Impairment of Fertility—Ziprasidone was shown to increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis) were mated with untreated females. In a 6-month study in male rats given 200 mg/kg/day (10 times the MRHD on a mg/m^2 basis) there were no treatment-related findings observed in the testes.

Pregnancy - Pregnancy Category C—In animal studies ziprasidone demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses. When ziprasidone was administered to pregnant rabbits during the period of organogenesis, an increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) was observed at a dose of 30 mg/kg/day (3 times the MRHD of 200 mg/day on a mg/m^2 basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD on a mg/m^2 basis) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg/day (2 and 8 times the MRHD on a mg/m^2 basis) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis).

There was an increase in the number of pups born dead and a decrease in postnatal survival through the first 4 days of lactation among the offspring of female rats treated during gestation and lactation with doses of 10 mg/kg/day (0.5 times the MRHD on a mg/m^2 basis) or greater. Offspring developmental delays and neurobehavioral functional impairment were observed at doses of 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis) or greater. A no-effect level was not established for these effects.

There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery—The effect of ziprasidone on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether, and if so in what amount, ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breast feed.

Pediatric Use—The safety and effectiveness of ziprasidone in pediatric patients have not been established.

Geriatric Use—Of the approximately 4500 patients treated with ziprasidone in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability of ziprasidone or for reduced clearance of ziprasidone in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

ADVERSE REACTIONS

Premarketing experience

The premarketing development program for oral ziprasidone included approximately 5700 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5700, over 4800 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1831 patient-years. These patients include: (1) 4331 patients who participated in multiple-dose trials, predominantly in schizophrenia, representing approximately 1698 patient-years of exposure as of February 5, 2000; and (2) 472 patients who participated in bipolar mania trials representing approximately 133 patient-years of exposure. The conditions and duration of treatment with ziprasidone included open-label and double-blind studies, inpatient and outpatient studies, and short-term and longer-term exposure.

The premarketing development program for intramuscular ziprasidone included 570 patients and/or normal subjects who received one or more injections of ziprasidone. Over 325 of these subjects participated in trials involving the administration of multiple doses.

Adverse events during exposure were obtained by collecting voluntarily reported adverse experiences, as well as results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Oral Ziprasidone

The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which ziprasidone was administered in doses ranging from 10 to 200 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Oral Ziprasidone

Schizophrenia—Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients (see **PRECAUTIONS**).

Bipolar Mania—Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among ziprasidone patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events.

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials—The most commonly observed adverse events associated with the use of ziprasidone (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (ziprasidone incidence at least twice that for placebo) are shown in Tables 1 and 2.

Continued on next page

Geodon—Cont.

Table 1: Common Treatment-Emergent Adverse Events Associated with the Use of Ziprasidone in 4- and 6-Week Trials—SCHIZOPHRENIA

	Percentage of Patients Reporting Event	
Adverse Event	Ziprasidone (N=702)	Placebo (N=273)
Somnolence	14	7
Respiratory Tract Infection	8	3

Table 2: Common Treatment-Emergent Adverse Events Associated with the Use of Ziprasidone in 3-Week Trials—BIPOLAR MANIA

	Percentage of Patients Reporting Event	
Adverse Event	Ziprasidone (N=279)	Placebo (N=136)
Somnolence	31	12
Extrapyramidal Symptoms*	31	12
Dizziness**	16	7
Akathisia	10	5
Abnormal Vision	6	3
Asthenia	6	2
Vomiting	5	2

* Extrapyramidal Symptoms includes the following adverse event terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse events occurred individually at an incidence greater than 10% in bipolar mania trials.

**Dizziness includes the adverse event terms dizziness and lightheadedness.

Adverse Events Occurring at an Incidence of 2% or More Among Ziprasidone-Treated Patients in Short-Term, Oral, Placebo-Controlled Trials

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) in predominantly patients with schizophrenia, including only those events that occurred in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

Table 3. Treatment-Emergent Adverse Event Incidence In Short-Term Oral Placebo-Controlled Trials—SCHIZOPHRENIA

	Percentage of Patients Reporting Event	
Body System/Adverse Event	Ziprasidone (N=702)	Placebo (N=273)
Body as a Whole		
Asthenia	5	3
Accidental Injury	4	2
Chest Pain	3	2
Cardiovascular		
Tachycardia	2	1
Digestive		
Nausea	10	7
Constipation	9	8
Dyspepsia	8	7
Diarrhea	5	4
Dry Mouth	4	2
Anorexia	2	1
Nervous		
Extrapyramidal Symptoms*	14	8
Somnolence	14	7
Akathisia	8	7
Dizziness**	8	6
Respiratory		
Respiratory Tract Infection	8	3
Rhinitis	4	2
Cough Increased	3	1
Skin and Appendages		
Rash	4	3
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	3	2

* Extrapyramidal Symptoms includes the following adverse event terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse events occurred individually at an incidence greater than 5% in schizophrenia trials.

**Dizziness includes the adverse event terms dizziness and lightheadedness.

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 3 weeks) in patients with bipolar mania, including only those events that occurred in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

Table 4. Treatment-Emergent Adverse Event Incidence In Short-Term Oral Placebo-Controlled Trials—BIPOLAR MANIA

	Percentage of Patients Reporting Event	
Body System/Adverse Event	Ziprasidone (N=279)	Placebo (N=136)
Body as a Whole		
Headache	18	17
Asthenia	6	2
Accidental Injury	4	1
Cardiovascular		
Hypertension	3	2
Digestive		
Nausea	10	7
Diarrhea	5	4
Dry Mouth	5	4
Vomiting	5	2
Increased Salivation	4	0
Tongue Edema	3	1
Dysphagia	2	0
Musculoskeletal		
Myalgia	2	0
Nervous		
Somnolence	31	12
Extrapyramidal Symptoms*	31	12
Dizziness**	16	7
Akathisia	10	5
Anxiety	5	4
Hypesthesia	2	1
Speech Disorder	2	0
Respiratory		
Pharyngitis	3	1
Dyspnea	2	1
Skin and Appendages		
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	6	3

* Extrapyramidal Symptoms includes the following adverse event terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse events occurred individually at an incidence greater than 10% in bipolar mania trials.

**Dizziness includes the adverse event terms dizziness and lightheadedness.

Explorations for interactions on the basis of gender did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of this demographic factor.

Dose Dependency of Adverse Events in Short-Term, Fixed-Dose, Placebo-Controlled Trials

An analysis for dose response in the schizophrenia 4-study pool revealed an apparent relation of adverse event to dose for the following events: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision.

Extrapyramidal Symptoms (EPS)—The incidence of reported EPS (which included the adverse event terms extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching) for ziprasidone-treated patients in the short-term, placebo-controlled schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo.

Vital Sign Changes—Ziprasidone is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain—The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 4- and 6-week placebo-controlled schizophrenia clinical trials, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. In this set of clinical trials, weight gain was reported as an adverse event in 0.4% and 0.4% of ziprasidone and placebo patients, respectively. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (>7% of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients who entered the program with a "high" BMI.

ECG Changes—Ziprasidone is associated with an increase in the QTc interval (see **WARNINGS**). In the schizophrenia trials, ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients.

Other Adverse Events Observed During the Premarketing Evaluation of Oral Ziprasidone

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with ziprasidone in schizophrenia trials at multiple doses >4 mg/day within the database of 3834 patients. All reported events are included except those already listed in Table 3 or elsewhere in labeling, those event terms that were so general as to be uninformative, events reported only once and that did not have a substantial probability of being acutely life-threatening, events that are part of the illness being treated or are otherwise common as background events, and events considered unlikely to be drug-related. It is important to emphasize that, although the events reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident.

Cardiovascular System: *Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis.

Digestive System: *Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, chole-

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Endocrine: *Rare:* hypothyroidism, hyperthyroidism, thyroiditis.

Hemic and Lymphatic System: *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia.

Metabolic and Nutritional Disorders: *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia; hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis.

Musculoskeletal System: *Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy.

Nervous System: *Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus.

Respiratory System: *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus.

Skin and Appendages: *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash.

Special Senses: *Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis.

Urogenital System: *Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage.

Adverse Findings Observed in Trials of Intramuscular Ziprasidone

Adverse Events Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term Trials of Intramuscular Ziprasidone

Table 5 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy with intramuscular ziprasidone in 1% or more of patients.

In these studies, the most commonly observed adverse events associated with the use of intramuscular ziprasidone (incidence of 5% or greater) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%).

[See table 5 at right].

Other Events Observed During Post-marketing Use

Adverse event reports not listed above that have been received since market introduction include rare occurrences of the following (no causal relationship with ziprasidone has been established): *Cardiac Disorders:* Tachycardia, Torsade de Pointes (in the presence of multiple confounding factors - see WARNINGS); *Reproductive System and Breast Disorders:* galactorrhea; *Nervous System Disorders:* Neuroleptic malignant syndrome; *Psychiatric Disorders:* Insomnia; *Skin and subcutaneous Tissue Disorders:* Allergic reaction, rash; *Vascular Disorders:* Postural hypotension.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class—Ziprasidone is not a controlled substance.

Physical and Psychological Dependence—Ziprasidone has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which ziprasidone will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ziprasidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience—In premarketing trials involving more than 5400 patients and/or normal subjects, accidental or intentional overdosage of oral ziprasidone was documented in 10 patients. All of these patients survived without sequelae. In the patient taking the largest confirmed amount, 3240 mg, the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

In post-marketing use, adverse events reported in association with ziprasidone overdose generally included extrapyramidal symptoms, somnolence, tremor, and anxiety. The largest confirmed post-marketing single ingestion was 12,800 mg; extrapyramidal symptoms and a QTc interval of 446 msec were reported with no cardiac sequelae.

TABLE 5. Treatment-Emergent Adverse Event Incidence in Short-Term Fixed-Dose Intramuscular Trials

	Percentage of Patients Reporting Event		
Body System/Adverse Event	Ziprasidone 2 mg (N=92)	Ziprasidone 10 mg (N=63)	Ziprasidone 20 mg (N=41)
Body as a Whole			
Headache	3	13	5
Injection Site Pain	9	8	7
Asthenia	2	0	0
Abdominal Pain	0	2	0
Flu Syndrome	1	0	0
Back Pain	1	0	0
Cardiovascular			
Postural Hypotension	0	0	5
Hypertension	2	0	0
Bradycardia	0	0	2
Vasodilation	1	0	0
Digestive			
Nausea	4	8	12
Rectal Hemorrhage	0	0	2
Diarrhea	3	3	0
Vomiting	0	3	0
Dyspepsia	1	3	2
Anorexia	0	2	0
Constipation	0	0	2
Tooth Disorder	1	0	0
Dry Mouth	1	0	0
Nervous			
Dizziness	3	3	10
Anxiety	2	0	0
Insomnia	3	0	0
Somnolence	8	8	20
Akathisia	0	2	0
Agitation	2	2	0
Extrapyramidal Syndrome	2	0	0
Hypertonia	1	0	0
Cogwheel Rigidity	1	0	0
Paresthesia	0	2	0
Personality Disorder	0	2	0
Psychosis	1	0	0
Speech Disorder	0	2	0
Respiratory			
Rhinitis	1	0	0
Skin and Appendages			
Furunculosis	0	2	0
Sweating	0	0	2
Urogenital			
Dysmenorrhea	0	2	0
Priapism	1	0	0

Management of Overdosage—In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Intravenous access should be established and gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects that might be additive to those of ziprasidone.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, epinephrine and dopamine should not be used, since beta stimulation combined with α_1 antagonism associated with

Continued on next page

Geodon—Cont.

ziprasidone may worsen hypotension. Similarly, it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of ziprasidone, resulting in problematic hypotension.

In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. There is no specific antidote to ziprasidone, and it is not dialyzable. The possibility of multiple drug involvement should be considered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

When deciding among the alternative treatments available for schizophrenia, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs (see **WARNINGS**).

Initial Treatment

GEODON® Capsules should be administered at an initial daily dose of 20 mg BID with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg BID. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, ordinarily patients should be observed for improvement for several weeks before upward dosage adjustment.

Efficacy in schizophrenia was demonstrated in a dose range of 20 to 100 mg BID in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 to 80 mg BID, but results were not consistent. An increase to a dose greater than 80 mg BID is not generally recommended. The safety of doses above 100 mg BID has not been systematically evaluated in clinical trials.

Maintenance Treatment

While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, systematic evaluation of ziprasidone has shown that its efficacy in schizophrenia is maintained for periods of up to 52 weeks at a dose of 20 to 80 mg BID (see **CLINICAL PHARMACOLOGY**). No additional benefit was demonstrated for doses above 20 mg BID. Patients should be periodically reassessed to determine the need for maintenance treatment.

Bipolar Mania

Initial Treatment

Oral ziprasidone should be administered at an initial daily dose of 40 mg BID with food. The dose should then be increased to 60 mg or 80 mg BID on the second day of treatment and subsequently adjusted on the basis of toleration and efficacy within the range 40-80 mg BID. In the flexible-dose clinical trials, the mean daily dose administered was approximately 120 mg (see **CLINICAL PHARMACOLOGY**).

Maintenance Treatment

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of mania with ziprasidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of ziprasidone in such longer-term treatment (i.e., beyond 3 weeks).

Intramuscular Administration for Acute Agitation in Schizophrenia

The recommended dose is 10 to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied.

If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible.

Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

Dosing in Special Populations

Oral: Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment.

Intramuscular: Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race.

Preparation for Administration

GEODON® for Injection (ziprasidone mesylate) should only be administered by intramuscular injection. Single-dose vials require reconstitution prior to administration; any unused portion should be discarded.

Add 1.2 mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. To administer a 10 mg dose, draw up 0.5 mL of the reconstituted solution. To administer a 20 mg dose, draw up 1.0 mL of the reconstituted solution. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

GEODON® Capsules are differentiated by capsule color/size and are imprinted in black ink with "Pfizer" and a unique number. GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:

GEODON® Capsules

Package Configuration	Capsule Strength (mg)	NDC Code	Imprint
Bottles of 60	20	NDC-0049-3960-60	396
Bottles of 60	40	NDC-0049-3970-60	397
Bottles of 60	60	NDC-0049-3980-60	398
Bottles of 60	80	NDC-0049-3990-60	399
Unit dose/80	20	NDC-0049-3960-41	396
Unit dose/80	40	NDC-0049-3970-41	397
Unit dose/80	60	NDC-0049-3980-41	398
Unit dose/80	80	NDC-0049-3990-41	399

Storage and Handling— GEODON® Capsules should be stored at controlled room temperature, 15°-30°C (59°-86°F).

GEODON® for Injection is available in a single dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions—see **Preparation for Administration**) for intramuscular administration. Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

GEODON® for Injection

Package	Concentration	NDC Code
Single Use Vials	20 mg/mL	NDC-0049-3920-83

Storage and Handling— GEODON® for Injection should be stored at controlled room temperature, 15°-30°C (59°-86°F) in dry form. Protect from light. Following reconstitution, GEODON for Injection can be stored, when protected from light, for up to 24 hours at 15°-30°C (59°-86°F) or up to 7 days refrigerated, 2°-8°C (36°-46°F).

Rx only

Distributed by
Pfizer Roerig
Division of Pfizer Inc, NY, NY 10017
LAB-0273-7.0 Revised May 2005

Shown in Product Identification Guide, page 329

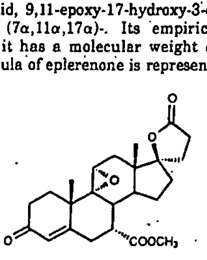
INSPRA® ℞

[In-sprā]
(eplerenone) tablets

DESCRIPTION

INSPRA contains eplerenone, a blocker of aldosterone binding at the mineralocorticoid receptor.

Eplerenone is chemically described as Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ-lactone, methyl ester, (7α,11α,17α)-. Its empirical formula is $C_{24}H_{30}O_6$ and it has a molecular weight of 414.50. The structural formula of eplerenone is represented below:



eplerenone

Eplerenone is an odorless, white to off-white crystalline powder. It is very slightly soluble in water, with its solubility essentially pH independent. The octanol/water partition coefficient of eplerenone is approximately 7.1 at pH 7.0.

INSPRA for oral administration contains 25 mg or 50 mg of eplerenone and the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hypromellose, sodium lauryl sulfate, talc, magnesium stearate, titanium dioxide, polyethylene glycol, polysorbate 80, and iron oxide yellow and iron oxide red.

CLINICAL PHARMACOLOGY

Mechanism of Action

Eplerenone binds to the mineralocorticoid receptor and blocks the binding of aldosterone, a component of the renin-angiotensin-aldosterone-system (RAAS). Aldosterone synthesis, which occurs primarily in the adrenal gland, is modulated by multiple factors, including angiotensin II and non-RAAS mediators such as adrenocorticotropic hormone (ACTH) and potassium. Aldosterone binds to mineralocorticoid receptors in both epithelial (e.g., kidney) and nonepithelial (e.g., heart, blood vessels, and brain) tissues and increases blood pressure through induction of sodium reabsorption and possibly other mechanisms.

Eplerenone has been shown to produce sustained increases in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. The resulting increased plasma renin activity and aldosterone circulating levels do not overcome the effects of eplerenone.

Eplerenone selectively binds to recombinant human mineralocorticoid receptors relative to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

Pharmacokinetics

General: Eplerenone is cleared predominantly by cytochrome P450 (CYP) 3A4 metabolism, with an elimination half-life of 4 to 6 hours. Steady state is reached within 2 days. Absorption is not affected by food. Inhibitors of CYP3A4 (e.g., ketoconazole, saquinavir) increase blood levels of eplerenone.

Absorption and Distribution: Mean peak plasma concentrations of eplerenone are reached approximately 1.5 hours following oral administration. The absolute bioavailability of eplerenone is unknown. Both peak plasma levels (C_{max}) and area under the curve (AUC) are dose proportional for doses of 25 to 100 mg and less than proportional at doses above 100 mg.

The plasma protein binding of eplerenone is about 50% and it is primarily bound to alpha 1-acid glycoproteins. The apparent volume of distribution at steady state ranged from 43 to 90 L. Eplerenone does not preferentially bind to red blood cells.

Metabolism and Excretion: Eplerenone metabolism is primarily mediated via CYP3A4. No active metabolites of eplerenone have been identified in human plasma.

Less than 5% of an eplerenone dose is recovered as unchanged drug in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 32% of the dose was excreted in the feces and approximately 67% was excreted in the urine. The elimination half-life of eplerenone is approximately 4 to 6 hours. The apparent plasma clearance is approximately 10 L/hr.

Special Populations

Age, Gender, and Race: The pharmacokinetics of eplerenone at a dose of 100 mg once daily have been investigated in the elderly (≥65 years), in males and females, and in blacks. The pharmacokinetics of eplerenone did not differ significantly between males and females. At steady state, elderly subjects had increases in C_{max} (22%) and AUC (45%) compared with younger subjects (18 to 45 years). At steady state, C_{max} was 19% lower and AUC was 26% lower in blacks. (See **PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Geriatric Use** and **DOSAGE AND ADMINISTRATION, Hypertension.**)

Renal Insufficiency: The pharmacokinetics of eplerenone were evaluated in patients with varying degrees of renal insufficiency and in patients undergoing hemodialysis. Compared with control subjects, steady-state AUC and C_{max} were increased by 38% and 24%, respectively, in patients with severe renal impairment and were decreased by 26% and 3%, respectively, in patients undergoing hemodialysis. No correlation was observed between plasma clearance of eplerenone and creatinine clearance. Eplerenone is not removed by hemodialysis. (See **WARNINGS, Hyperkalemia in Patients Treated for Hypertension** and **PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure Post-Myocardial Infarction and Congestive Heart Failure Post-Myocardial Infarction and Hypertension.**)

Hepatic Insufficiency: The pharmacokinetics of eplerenone 400 mg have been investigated in patients with moderate (Child-Pugh Class B) hepatic impairment and compared with normal subjects. Steady-state C_{max} and AUC of eplerenone were increased by 3.6% and 42%, respectively. (See **DOSAGE AND ADMINISTRATION, Hypertension.**)

Heart Failure: The pharmacokinetics of eplerenone 50 mg were evaluated in 8 patients with heart failure (NYHA classification II-IV) and 8 matched (gender, age, weight) healthy controls. Compared with the controls, steady state AUC and C_{max} in patients with stable heart failure were 38% and 30% higher, respectively.

Drug-Drug Interactions

(See **PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions.**)

Drug-drug interaction studies were conducted with a 100 mg dose of eplerenone.

Eplerenone is metabolized primarily by CYP3A4. A potent inhibitor of CYP3A4 (ketoconazole) caused increased exposure of about 5-fold while less potent CYP3A4 inhibitors (erythromycin, saquinavir, verapamil, and fluconazole) gave

Depression can recur many times...

Or not.

Extending the body of evidence

2-YEAR RECURRENCE PREVENTION data for EFFEXOR XR[1]

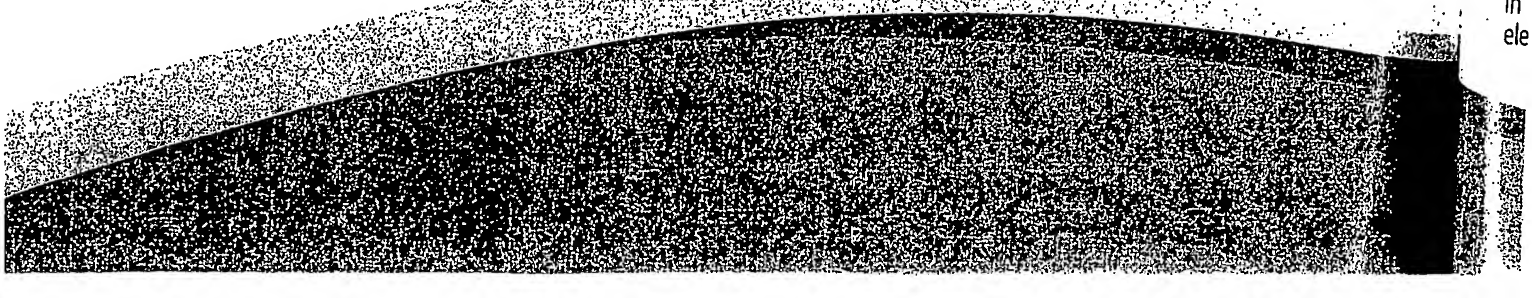
IMPORTANT TREATMENT CONSIDERATIONS

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with Major Depressive Disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

- EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI; at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.



CLINICAL DATA

Length and results of positive, randomized, double-blind, placebo-controlled antidepressant clinical studies[1]

	6 months	1 year	2 years
EFFEXOR XR® (venlafaxine HCl)	✓	✓	✓
Cymbalta® (duloxetine HCl)	✓		
Lexapro® (escitalopram oxalate)	✓	✓	
Wellbutrin XL® (bupropion HCl)	✓		
Zoloft® (sertraline HCl)	✓	✓	*
Paxil® (paroxetine HCl)	✓	✓	†

✓ = demonstrated relapse/recurrence prevention at end point.

Zoloft has been studied in 2-year recurrence prevention as monotherapy but failed to show a significant difference vs. placebo at end point. Wilson KCM, et al.** ***Br J Psychiatry. **2003;182:492-497.**

†Paxil has been studied in 2-year recurrence prevention in combination with psychotherapy/clinical management sessions with or without augmentation, but not as monotherapy. In patients with recurrent depression, no significant difference was seen between Paxil and placebo. Reynolds CF, et al. ***N Engl J Med.*** **2006;354:1130-1138.**

In the EFFEXOR XR PREVENT study, patients had at least 3 prior episodes of depression in their lifetime.

EFFEXOR® and EFFEXOR XR® are registered trademarks of Wyeth Pharmaceuticals Inc.

Other brands listed are the trademarks of their respective owners and are not trademarks of Wyeth Pharmaceuticals Inc.

- Adult and pediatric patients with MDD can experience worsening of their depression and/or the emergence of suicidal ideation and behavior, whether or not they are taking antidepressants. **Patients treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, or at the time of increases or decreases in dose.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported and may represent precursors to emerging suicidality. Stopping or modifying therapy should be considered especially when symptoms are severe, abrupt in onset, or not part of presenting symptoms.
- The development of potentially life-threatening serotonin syndrome may occur when EFFEXOR XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems. Concomitant use of EFFEXOR XR with MAOIs is contraindicated. If concomitant use of EFFEXOR XR with an SSRI, SNRI, or a triptan is clinically warranted, careful observation of the patient is advised. Concomitant use of EFFEXOR XR with tryptophan supplements is not recommended.
- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.
- Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually. See the Precautions section of the Prescribing Information.

Please see brief summary of Prescribing Information on adjacent pages.

ONCE-DAILY
VENLAFAXINE HCl
EFFEXOR XR® *EXTENDED RELEASE CAPSULES*

The change they deserve.

Take a closer look at

Dialogues

Time to Talk™

Dialogues is a unique patient support and education program that is designed to help you foster successful therapy

Dialogues offers patients access to a call center to speak with a health care provider for patient support and education to reinforce your efforts

supplies feedback and updates about these patient calls to you, their physician

Encourage your **EFFEXOR XR** patients to enroll in ***Dialogues*** by calling 866-[illegible] — and you can visit **mddpatientsupport.com**

- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled depression, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence ≥10% and ≥2× that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

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The change they deserve

Reference: 1. Data on file, Wyeth Pharmaceuticals Inc.

Please see brief summary of Prescribing Information on adjacent pages.

Wyeth®

ONCE-DAILY
VENLAFAXINE HCl
EFFEXOR XR® EXTENDED RELEASE CAPSULES

BRIEF SUMMARY. See package insert for full prescribing information.

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with Major Depressive Disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). WARNINGS: **Clinical Worsening and Suicide Risk**—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with MDD and other psychiatric disorders. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. **All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Adults with MDD or comorbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD and other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). **Families and caregivers of pediatric patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. Prior to initiating antidepressant treatment, patients with depressive symptoms should be screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Effexor XR is not approved for use in treating bipolar depression. **Potential for Interaction with MAOIs—Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine, or who recently discontinued venlafaxine prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Effexor XR should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine before starting an MAOI.** **Serotonin Syndrome**—The development of potentially life-threatening serotonin syndrome may occur with Effexor XR treatment, particularly with (i) concomitant use of serotonergic drugs and (ii) with drugs that impair metabolism of serotonin (see **CONTRAINDICATIONS—MAOIs**). If concomitant treatment of Effexor XR with an SSRI, SNRI, or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with serotonin precursors (such as tryptophan supplements) is not recommended. **Sustained Hypertension**—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular monitoring of BP is recommended. For patients experiencing sustained increase in BP, consider either dose reduction or discontinuation. *Mydriasis*: Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). PRECAUTIONS: General—*Discontinuation of Treatment with Effexor XR.* Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. *Insomnia and Nervousness*: Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to drug discontinuation in 1% of both depressed patients and Panic Disorder (PD) patients and in 3% of both Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 0% of SAD and PD patients. *Changes in Weight: Adult Patients*: In short-term MDD trials, 7% of Effexor XR patients had ≥5% loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had ≥7% loss of body weight, and 0.3% discontinued for weight loss in 8-week studies. In 12-week SAD trials, 3% of Effexor XR patients had ≥7% loss of body weight and no patients discontinued for weight loss. In 12-week PD trials, 3% of Effexor XR patients had ≥7% loss of body weight, and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. *Pediatric Patients*: Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both MDD and GAD studies (18% of Effexor XR patients vs. 3.6% of placebo patients; $P<0.001$) and the SAD study (47% of Effexor XR patients vs. 14% of placebo patients; $P<0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month MDD study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents ≥12 years old. *Changes in Height: Pediatric Patients*: In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm (n=122), while placebo patients grew an average of 1.0 cm (n=132); $P=0.041$. This difference in height increase was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm (n=146), while placebo patients grew an average of 0.7 cm (n=147). During the 16-week, placebo-controlled SAD study, both the Effexor XR (n=109) and the placebo (n=112) patients grew an average of 1.0 cm. In the 6-month MDD study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents ≥12 years old. *Changes in Appetite: Adult Patients*: Treatment-emergent anorexia was more commonly reported for

Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. *Pediatric Patients*: Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. In the placebo-controlled trial for SAD, 22% and 3% of patients aged 8-17 treated for up to 16 weeks with Effexor XR and placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving Effexor XR and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either Effexor XR or placebo. *Activation of Mania/Hypomania*: Mania or hypomania has occurred during short-term depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. *Hyponatremia*: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. *Seizures*: In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. *Abnormal Bleeding*: Abnormal bleeding (most commonly ecchymosis) has been reported. *Serum Cholesterol Elevation*: Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. *Use in Patients With Concomitant Illness*: Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient *Medication Guide About Using Antidepressants in Children and Teenagers* is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexorxr.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients 1) about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities; 2) to avoid alcohol while taking Effexor XR; and 3) about the risk of serotonin syndrome with the concomitant use of Effexor XR and triptans, tramadol, tryptophan supplements, or other serotonergic agents. Patients should be advised to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations and nutritional supplements they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena; or 4) if they have a history of glaucoma or increased intraocular pressure. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions**—*Alcohol*: A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. *Cimetidine*: Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. *Diazepam*: A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. *Haloperidol*: Venlafaxine decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination half-life was unchanged. *Lithium*: A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. *Drugs Highly Bound to Plasma Proteins*: Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. *Drugs That Inhibit Cytochrome P450 Isoenzymes*: CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. *Drugs Metabolized by Cytochrome P450 Isoenzymes*: Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. *Imipramine*: Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. *Risperidone*: Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4:** Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. *Indinavir*: In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2:** Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9:** Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19:** Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). *MAOIs*: See **CONTRAINDICATIONS** and **WARNINGS**. *CNS-Active Drugs*: Use caution with concomitant use of venlafaxine and other CNS-active drugs. **Serotonergic Drugs and Triptans (see WARNINGS: Serotonin Syndrome):** Based on the mechanism of action of Effexor XR and the potential for serotonin syndrome, caution is advised when Effexor XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's wort. If concomitant treatment of Effexor XR with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with tryptophan supplements is not recommended. *Electroconvulsive Therapy (ECT)*: There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—*Carcinogenesis*: There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m² basis. *Mutagenesis*: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. *Impairment of Fertility*: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m² basis. **Pregnancy**—*Teratogenic Effects—Pregnancy Category C.* Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m² basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. *Nonteratogenic Effects.* Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS-General**, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. Hyponatremia and SIADH have been reported, usually in the elderly. **ADVERSE REACTIONS:** *Associated with Discontinuation of Treatment*—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. *Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD*—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. *Vital Sign Changes*: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS-Sustained Hypertension**). *Laboratory Changes*: Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. *Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR*—N=6,670. "Frequent"=events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. Body as a whole - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. Cardiovascular system - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. Digestive system - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. Endocrine system - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. Hemic and lymphatic system - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. Metabolic and nutritional - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. Musculoskeletal system - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. Nervous system - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. Respiratory system - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. Skin and appendages - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. Special senses - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. Urogenital system - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports:** agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease (including pulmonary eosinophilia), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE:** Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE:** Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, liver necrosis, and death have been reported. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION:** Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C024, revised June 2006.

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ORIGINAL ARTICLE

Maintenance Treatment of Major Depression in Old Age

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ABSTRACT

BACKGROUND

Elderly patients with major depression, including those having a first episode, are at high risk for recurrence of depression, disability, and death.

METHODS

We tested the efficacy of maintenance paroxetine and monthly interpersonal psychotherapy in patients 70 years of age or older who had depression (55 percent of whom were having a first episode) in a 2-by-2, randomized, double-blind, placebo-controlled trial. Among patients with a response to treatment with paroxetine and psychotherapy, 116 were randomly assigned to one of four maintenance-treatment programs (either paroxetine or placebo combined with either monthly psychotherapy or clinical-management sessions) for two years or until the recurrence of major depression. Clinical-management sessions, conducted by the same nurses, social workers, and psychologists who provided psychotherapy, involved discussion of symptoms.

RESULTS

Major depression recurred within two years in 35 percent of the patients receiving paroxetine and psychotherapy, 37 percent of those receiving paroxetine and clinical-management sessions, 68 percent of those receiving placebo and psychotherapy, and 58 percent of those receiving placebo and clinical-management sessions (P=0.02). After adjustment for the effect of psychotherapy, the relative risk of recurrence among those receiving placebo was 2.4 times (95 percent confidence interval, 1.4 to 4.2) that among those receiving paroxetine. The number of patients needed to be treated with paroxetine to prevent one recurrence was 4 (95 percent confidence interval, 2.3 to 10.9). Patients with fewer and less severe coexisting medical conditions (such as hypertension or cardiac disease) received greater benefit from paroxetine (P=0.03 for the interaction between treatment with paroxetine and baseline severity of medical illness).

CONCLUSIONS

Patients 70 years of age or older with major depression who had a response to initial treatment with paroxetine and psychotherapy were less likely to have recurrent depression if they received two years of maintenance therapy with paroxetine. Monthly maintenance psychotherapy did not prevent recurrent depression. (ClinicalTrials.gov number, NCT00178100.)

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DEPRESSION HAS A STRONG TENDENCY to recur in elderly persons, with rates of recurrence of 50 to 90 percent over a period of two to three years[1]; hence, the goal of treatment is not only recovery but also the prevention of recurrence.[2] Finding practical and affordable depression-management strategies that prevent recurrence is of great importance.[3-6]

There are few data from controlled studies on the efficacy of maintenance antidepressant medication or depression-specific psychotherapy in patients 70 years of age or older. We have reported that maintenance nortriptyline, monthly interpersonal psychotherapy, and the two in combination[7] are superior to placebo plus clinical-management sessions in preventing recurrences among patients 59 years of age or older who have had multiple episodes.[8] Selective serotonin-reuptake inhibitors (SSRIs) have now become the first-line treatment for depression in the elderly because of their favorable side-effect profiles and low risk of complications after an overdose.[9] However, there is little information about the long-term efficacy of SSRIs or psychotherapy in the elderly, and the available data are conflicting.[10,11] There is also no consensus about whether long-term maintenance pharmacotherapy is appropriate after a first episode of depression; most experts support the use of only 6 to 12 months of continued treatment for patients who have a first episode of depression in old age.[9]

We assessed whether long-term antidepressant treatment would affect the recurrence of depression specifically in people 70 years of age or older, the majority of whom were having a first episode of depression, since this population is at high risk for recurrence, cognitive impairment, intercurrent medical illness, and suicide.[2]

METHODS

The study setting was a university-based clinic for the treatment of depression in elderly patients. The study was conducted after approval from the university's institutional review board. Between March 1, 1999, and February 28, 2003, we recruited 210 patients, 195 of whom started short-term treatment (Table 1). The patients were at least 70 years of age; met the criteria of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV),[12] for current major depression (nonpsychotic and nonbipolar), as determined according to the Structured Clinical Interview for DSM-IV Axis I Disorders, version 2.0[13]; and had a score of at least 15 on the 17-item Hamilton Rating Scale for Depression[14] (scores can range from 0 to 52, with higher scores indicating more severe depression) and at least 17 on the Folstein Mini–Mental State Examination[15] (scores can range from 0 to 30, with higher scores indicating better mental status). All patients provided written informed consent.

We screened 363 patients, 153 of whom were excluded and 210 of whom agreed to participate (Fig. 1). Of the 195 who began short-term treatment, 151 (77.4 percent) had a clinical response (i.e., a Hamilton score of 0 to 10 for 3 consecutive weeks) and began 16 weeks of continued treatment, which was intended to stabilize and further improve the clinical response. Of these 151 patients, 116 (76.8 percent) remained well and were randomly assigned to a two-year maintenance-treatment program.

During short-term treatment, 10 of 195 patients (5.1 percent) were withdrawn from the trial: 3 because of hyponatremia, 2 because of rash, and 1 each because of nausea, orthostasis, unsteady gait, confusion, and paresthesias. During continued treatment, 5 of 151 patients (3.3 percent) were withdrawn from the trial: 2 because of sexual dysfunction, 1 because of tremors, and 2 because of gastrointestinal symptoms. Two patients, both with preexisting cardiac disease, died after myocardial infarction (one each during short-term and continued treatment). No patient committed suicide.

The patients received open treatment with paroxetine and weekly psychotherapy; the dose of paroxetine was initially 10 mg per day and was titrated over an eight-week period to a maximum of 40 mg per day. After having a response, the patients began 16 weeks of open continued treatment consisting of paroxetine and psychotherapy, with paroxetine continued at the same dose but with the frequency of psychotherapy decreasing to once every 2 weeks. As detailed elsewhere,[16,17] 69 patients received augmented pharmacotherapy with bupropion, nortriptyline, or lithium. If successful, augmented pharmacotherapy was continued for the remainder of a patient's participation unless he or she was randomly assigned to placebo during maintenance therapy. Thirty-eight of the 69 patients receiving augmented pharmacotherapy participated in the maintenance phase

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Patients Starting Short-Term Treatment (N=195)	Patients Starting Maintenance Treatment (N=116)†			
		Paroxetine + Psychotherapy (N=28)	Paroxetine + Clinical Management (N=35)	Placebo + Psychotherapy (N=35)	Placebo + Clinical Management (N=18)
Demographic characteristic					
Age at entry (yr)	77.1±5.6	77.6±7.0	77.0±5.9	77.4±5.0	74.8±4.4
Female sex (%)	66	68	60	71	56
White race (%)‡	91	93	91	94	94
Married (%)	41	50	40	49	39
Yr of education	12.9±2.9	13.3±3.7	12.9±2.5	12.4±2.9	13.3±2.4
Clinical characteristic					
Recurrent episode (%)	45	43	40	40	39
Age at onset of major depression (yr)	63.0±18.7	66.4±19.6	63.7±18.1	62.0±20.1	61.2±19.4
Median duration of current episode (wk)	39	57	26	36	43
Hamilton Rating Scale for Depression score§					
At baseline	20.5±3.6	20.6±4.2	19.5±2.7	20.3±3.3	19.8±2.4
At randomization		6.0±2.9	4.9±2.7	5.5±2.7	5.8±2.2
Cumulative Illness Rating Scale score¶	10.0±4.1	10.5±4.1	9.5±4.6	9.7±3.8	8.6±3.7
Folstein Mini–Mental State Examination score‖	27.8±2.5**	27.7±3.1	27.5±2.5	28.0±2.4	28.7±1.1
Mattis Dementia Rating Scale††					
Score	131.5±10.0**	131.3±14.0	130.7±9.6	131.7±9.1	134.4±8.1
Scaled score	8.5±3.2				
Brief Symptom Inventory Anxiety subscale score‡‡	1.16±0.86§§	1.13±1.02	1.12±0.89	1.13±0.81	0.82±0.67
Pittsburgh Sleep Quality Index score¶¶	10.5±4.1	11.9±4.5	10.0±3.8	10.1±4.1	10.5±4.5

* Plus–minus values are means ±SD.
† There are no significant differences between groups.
‡ Race was self-reported by the patients.
§ Scores for the 17-item Hamilton Rating Scale for Depression range from 0 to 52, with higher scores indicating more severe depression.
¶ Scores for the Cumulative Illness Rating Scale for Geriatrics range from 0 to 52, with higher scores indicating worse health status.
‖ Scores for the Folstein Mini–Mental State Examination range from 0 to 30, with higher scores indicating better mental status.
** The value is based on 193 patients.
†† Scores for the Mattis Dementia Rating Scale range from 0 to 144, with higher scores indicating better cognitive function.
‡‡ Scores for the Brief Symptom Inventory Anxiety subscale range from 0 to 3, with higher scores indicating worse condition.
§§ The value is based on 179 patients.
¶¶ Scores for the Pittsburgh Sleep Quality Index range from 0 to 21, with higher scores indicating a poorer quality of sleep.

of the study, with 19 randomly assigned to paroxetine and 19 to placebo.

Patients who made a full or a partial recovery were randomly assigned to one of four maintenance treatments: paroxetine plus monthly clinical-management sessions, placebo plus monthly clinical-management sessions, paroxetine plus monthly psychotherapy, and placebo plus monthly psychotherapy. The paroxetine, placebo, and augmented-pharmacotherapy tablets were identical in size, weight, and appearance. For patients assigned to maintenance placebo, the paroxetine dose was slowly tapered (together with the dose of any augmented pharmacotherapy) over a period of six weeks under double-blind conditions until discontinuation of the medication. The patients continued to receive maintenance therapy for two years or until recurrence of major depres-

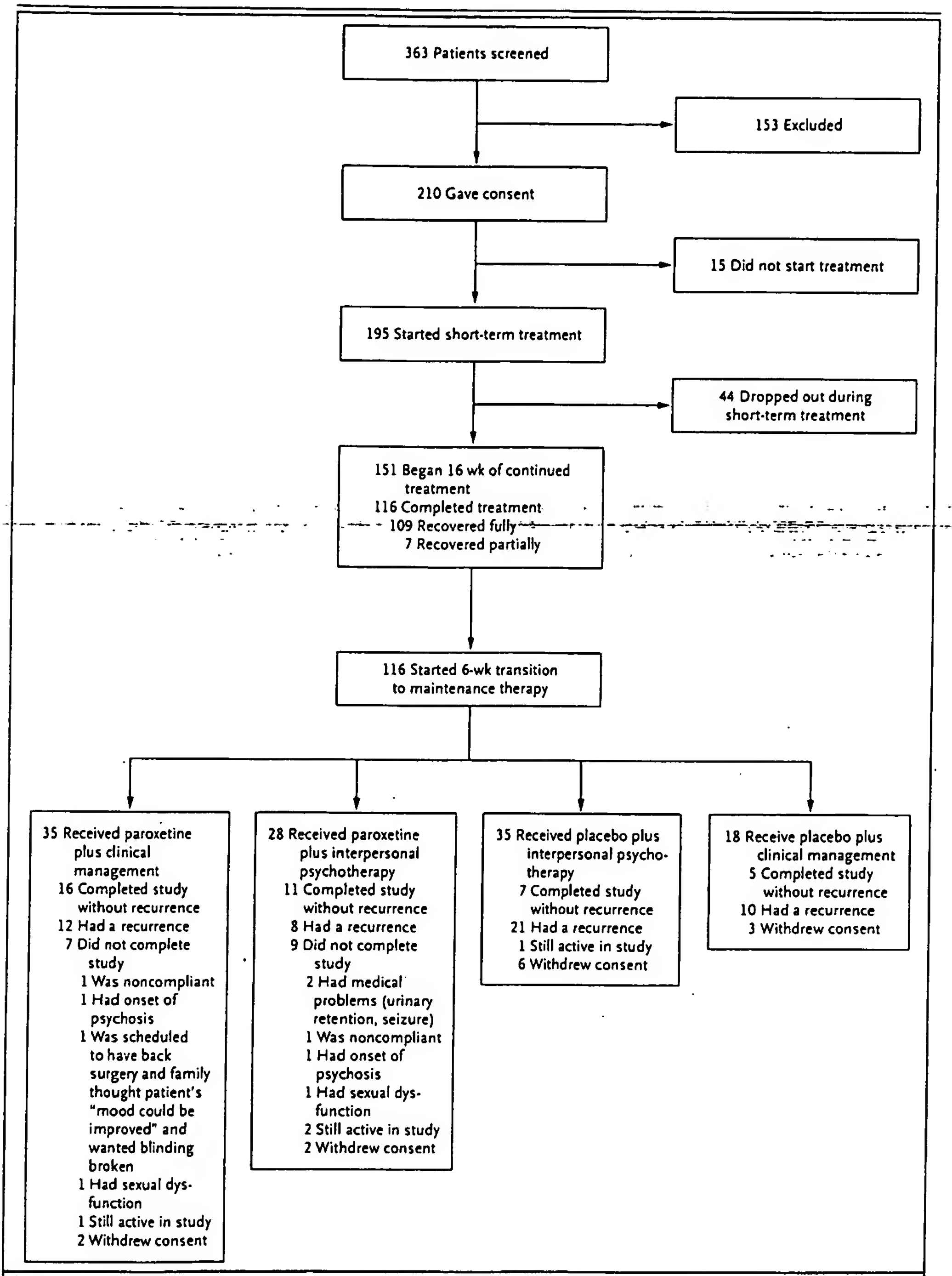

Figure 1. Enrollment and Outcomes.

sion. At the time of data analysis, four patients were still receiving maintenance therapy and had not yet completed two years of therapy; data from these patients were treated as censored observations.

The randomization schedule was generated by a project statistician at the beginning of the trial. Randomization was stratified according to the number of episodes (single vs. multiple), use of augmented pharmacotherapy, and level of cogni-

tive impairment (a score of more than 130 vs. a score of 130 or less on the Mattis Dementia Rating Scale [scores can range from 0 to 144, with higher scores indicating better cognitive function]). Randomization was blocked to adjust cell sizes over the study period. The treatment team and outcome assessors were unaware of the patients' treatment assignments, and only the research pharmacist and the open-monitoring committee knew which patients were assigned to paroxetine and which to placebo.

The patients were seen monthly by the same clinician (a nurse, social worker, or psychologist) who had treated them during short-term and continued treatment. Patients assigned to clinical management were seen for 30-minute visits; they received no specific psychotherapy but were asked about symptoms and any possible adverse effects. The same clinicians conducted clinical-management sessions and psychotherapy. At each visit, orthostatic blood pressure and pulse were measured, body weight was recorded, and clinical ratings were performed with the use of the Hamilton Rating Scale for Depression.[17] Patients assigned to monthly psychotherapy were seen for 45-minute sessions. In order to ensure fidelity to manual-based treatment-delivery procedures, all clinical-management and psychotherapy sessions were audiotaped so that elements specific to interpersonal psychotherapy and to medical management could be rated in a blinded fashion.[18] The clinicians encouraged and monitored adherence by education of patients and family members, pill counts, and reminders at each clinic visit.

Recurrence of a major depressive episode, as defined by DSM-IV criteria and a Hamilton score of at least 15, was determined by administration of the Structured Clinical Interview for DSM-IV Axis I Disorders, version 2.0,[13] and independently confirmed clinically by a geriatric psychiatrist. Assessment of possible recurrence was performed as needed at any point during maintenance treatment. Both assessors were unaware of patients' treatment assignments. GlaxoSmithKline provided paroxetine tablets for use in this research study but had no other role in study design, data accrual, or data analysis.

STATISTICAL ANALYSIS

We estimated that the enrollment of 33 patients per active-treatment group and 20 patients in the placebo group (total, 119) would provide the study with a statistical power of at least 80 percent ($\alpha=0.05$) to detect a difference in recurrence rates of 60 percent between combined therapy and placebo and of 30 percent between each monotherapy and placebo. We assigned fewer patients to the placebo group because we hypothesized that the recurrence rate would be higher among patients receiving placebo and we wanted to maximize the number of observations in the active-treatment groups to test for pairwise differences in recurrence rates.

Our study hypothesis was that the four groups would differ from one another, and that the specific pattern of group differences would demonstrate the superiority of combined treatment (paroxetine plus interpersonal therapy) over each of the other three treatments and of either monotherapy over placebo plus clinical management. First, we used Kaplan–Meier survival analysis with log-rank chi-square statistics to test for overall differences in recurrence rates among the four maintenance treatments. We examined the survival curves stratified according to the number of episodes of major depression, level of cognitive impairment, and use of augmented pharmacotherapy. Second, to perform hypothesized pairwise contrasts, we used Cox proportional-hazards models with three dummy variables representing the four treatment groups. The Cox models tested for the effects of clinically relevant covariates on recurrence: the number and severity of concomitant medical illnesses (the "chronic medical burden"), as defined by scores for the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)[19] (range, 0 to 52, with higher scores indicating worse health status); anxiety, as defined by scores for the Brief Symptom Inventory Anxiety subscale[20] (range, 0 to 3, with higher scores indicating worse condition); cognitive impairment, as defined by scores for the Mattis Dementia Rating Scale[21]; and subjective sleep quality, as defined by scores for the Pittsburgh Sleep Quality Index[22] (range, 0 to 21, with higher scores indicating a poorer quality of sleep). We also used Cox models to test for moderation of maintenance-treatment effects on recurrence, as evidenced by interaction of treatment with each clinical covariate.

RESULTS

The four maintenance groups had similar demographic and clinical characteristics (Table 1). The

time from randomization to recurrence of depression (Fig. 2) differed among the four groups (P=0.02). The actuarial recurrence rates (after adjustment for censoring) were 35 percent among patients receiving paroxetine plus psychotherapy, 37 percent among those receiving paroxetine plus clinical-management sessions, 68 percent among those receiving placebo plus psychotherapy, and 58 percent among those receiving placebo plus clinical-management sessions. The Cochran–Mantel–Haenszel statistic for recurrence across the four groups stratified according to the receipt of augmented pharmacotherapy was also significant (P=0.03). The recurrence rates were higher among those who had received augmented pharmacotherapy (74 percent) than among those who had not (29 percent, P<0.001).

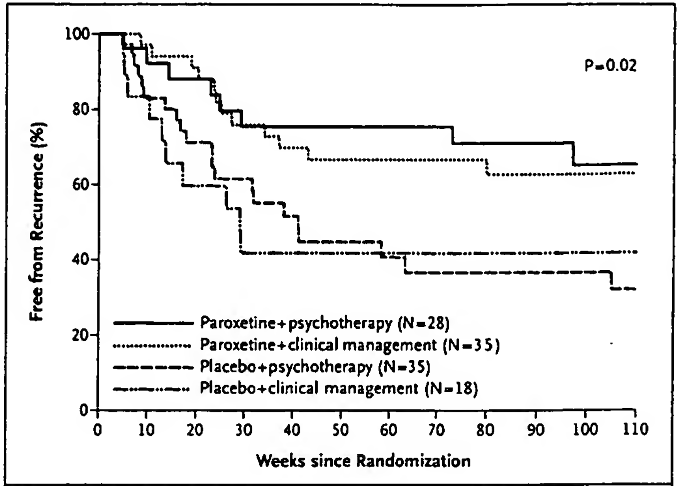

Figure 2. Time from Randomization to Recurrence.

The relative risk of recurrence among patients receiving placebo was 2.4 times that among patients receiving paroxetine (P=0.02; chi-square statistic=9.77 with 2 df). No effect of maintenance psychotherapy on recurrence was detected. Kaplan–Meier survival analysis with log-rank chi-square statistics was used to test for overall differences in recurrence rates among the groups. P values were based on the log-rank chi-square test.

A sensitivity analysis treating the four patients who had not yet completed two years of treatment at the time of the data analysis as having either completed the study without recurrence or as having had a recurrence of depression at the time of censoring yielded similar results to those shown in Figure 2 (P=0.02 and P=0.04, respectively).

Testing of hypothesized pairwise contrasts indicated that paroxetine plus psychotherapy was superior to placebo plus psychotherapy (P=0.03) and to placebo plus clinical management (P=0.05) in preventing recurrence. Similarly, paroxetine plus clinical management (without psychotherapy) was significantly more effective than placebo plus psychotherapy (P=0.03) and marginally more effective than placebo plus clinical management (P=0.06).

When recurrence outcomes among patients treated with paroxetine were compared with those among patients receiving placebo, after adjustment for psychotherapy status, the number of patients who needed to be treated with paroxetine to prevent one recurrence was 4 (95 percent confidence interval, 2.3 to 10.9). The relative risk of recurrence among patients receiving placebo was 2.4, as compared with those receiving paroxetine (95 percent confidence interval, 1.4 to 4.2).

In the subgroup of 69 patients enrolled during their first episode of depression, the recurrence rate among those receiving paroxetine (with or without psychotherapy) was 27 percent, as compared with 56 percent among those receiving placebo (with or without psychotherapy) (P=0.003). The recurrence rate among the 47 patients enrolled during a second or later episode of depression was 38 percent among those receiving paroxetine (with or without psychotherapy), as compared with 62 percent among those receiving placebo (with or without psychotherapy); the difference between the rates was not significant (P=0.22).

In Cox models, more severe anxiety (P=0.04), more numerous and more severe concomitant medical illnesses (P=0.02), and poorer sleep quality (P=0.001) all predicted a shorter period without depression. A significant interaction between the medical burden (as measured by the CIRS-G score) and drug assignment (P=0.03) indicated a moderating effect of the number and severity of coexisting medical illnesses on the long-term outcome. The hazard ratio for the interaction between drug assignment and CIRS-G score was 1.17 (95 percent confidence interval, 1.02 to 1.35), a value consistent with the presence of a small effect. (No moderation effect was found for cognition, anxiety, or sleep.) To illustrate the interaction of the number and severity of concomitant medical illnesses with pharmacotherapy, we dichotomized the CIRS-G scores at a mean value of 10 (Fig. 3); the results showed that patients with fewer and less severe concomitant medical illnesses fared better during paroxetine maintenance therapy than those with more

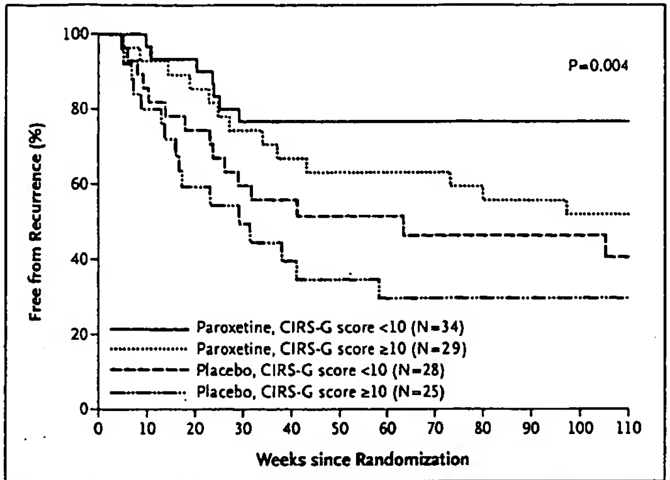

Figure 3. Effect of the Number and Severity of Concomitant Medical Illnesses on the Efficacy of Maintenance Therapy with Paroxetine.

Patients with a greater number of and more severe concomitant medical illnesses, as indicated by scores of 10 or more on the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), had higher rates of recurrent depression and did not fare as well during treatment with paroxetine as those with fewer and less severe concomitant medical illnesses. Although both paroxetine use and the score on the CIRS-G affected risk (main or direct effect, P=0.004), paroxetine was more effective in preventing recurrence in patients with fewer and less severe concomitant medical illnesses (interaction effect, P=0.03). Kaplan–Meier survival analysis with log-rank chi-square statistics was used to test for overall differences in recurrence rates among the groups. P values were based on the log-rank chi-square test.

numerous and more severe concomitant medical illnesses.

DISCUSSION

Our data provide support for the use of maintenance SSRI pharmacotherapy, but not interpersonal psychotherapy, to prevent recurrent depression in people 70 years of age or older, including those with a first episode of depression. To date, there has been no consensus about the appropriateness of long-term maintenance treatment for a first episode of depression in elderly patients, with most experts calling for only 6 to 12 months of continued treatment.[9]

We identified 10 published double-blind, placebo-controlled, maintenance trials of SSRIs and other nontricyclic antidepressants in adult patients,[23-32] but only 2 studies among patients 65 years of age or older.[10,11] All 10 studies in adults had positive findings, but the results of studies in elderly patients were mixed. Klysner et al.[10] demonstrated the maintenance efficacy of citalopram, whereas Wilson et al.[11] failed to find a difference between sertraline and placebo. In the study by Klysner et al., 85 percent of 121 participants (mean age, 74 to 75 years) were having their first episode of major depression. Among the 60 patients randomly assigned to citalopram, 19 (32 percent) had a recurrence during the 48-week maintenance-treatment period, as compared with 41 of the 61 patients receiving placebo (67 percent). Our data from patients receiving paroxetine replicate these findings and extend them to patients receiving two years of maintenance treatment, thereby adding substantially to the body of knowledge regarding long-term treatment strategies in elderly depressed people, especially those with a single episode of major depression. To place our observation within a broader medical context, the number of patients needed to be treated with paroxetine for two years to prevent a recurrence of depression is 4; in comparison, four large trials[33] of statins, which are widely used for the prevention of a second myocardial infarction, found that the number of patients needed to be treated with statins for five years to prevent another myocardial infarction was 21.

Our results are also noteworthy because few data from controlled studies provide support for the short-term efficacy of SSRIs in late-life depression. Only two published randomized, controlled trials of any SSRI in older adults, both of which used fluoxetine, are included in the Cochrane Database of Systematic Reviews (most recent update, February 25, 2005).[34] For short-term treatment, the pooled results give a number needed to treat of 8.5. In a large, eight-week, placebo-controlled trial of sertraline in the elderly, the adjusted mean difference between groups in scores on the Hamilton Rating Scale for Depression was only 1.5 points at the end of the study.[35] The only other published study of short-term SSRI treatment, a multisite, placebo-controlled trial of citalopram,[36] failed to demonstrate short-term efficacy in patients 75 years of age or older. In contrast to studies of short-term efficacy, our study supports the efficacy of maintenance therapy with SSRIs in preventing a recurrence of depression among people with first episodes in later life who have apparently benefited from initial SSRI treatment and interpersonal psychotherapy.

Contrary to our hypothesis, the current data failed to provide support for the efficacy of maintenance psychotherapy, despite the fact that we

had sufficient power to detect a clinically significant effect. The failure to demonstrate the efficacy of psychotherapy in the prevention of recurrence among patients 70 years of age or older could reflect differences between the patients in the current study and those in our earlier study,[8] since the psychotherapists who treated the patients were largely the same in both studies. The patients in the current study were, on average, 10 years older than those in the previous study (77 vs. 67 years) and had more cognitive impairment and coexisting medical illnesses. The results stand in contrast to those of previous studies that have demonstrated moderate prophylactic effects of psychotherapy in nongeriatric adults[37] and in the "young" elderly (mainly 60 to 75 years of age).[8] The patients in both previous studies had recurrent major depression, whereas the majority of patients in the current study had late-onset first episodes of depression. Late-onset depression occurs in a heterogeneous group of patients, some of whom may be in the preclinical stages of Alzheimer's disease or vascular dementia.[38] Their ability to learn and to modify their behavior (executive function) may be compromised; hence, psychotherapy for such patients may need to involve caregivers more extensively. More research is needed to address this issue as well as the use of other types of psychotherapy — such as problem-solving therapy — for such patients.[39] Moreover, all patients in the maintenance phase of our study had received psychotherapy during short-term treatment. The recurrence rates might have been higher among patients receiving maintenance SSRI therapy who were not initially treated with psychotherapy.

Given that the number and severity of concomitant medical illnesses (especially hypertension, coronary artery disease, diabetes, hyperlipidemia, osteoarthritis, and chronic lung disease) also affected the risk of recurrence and exerted a slight moderating effect on the response to long-term antidepressant treatment, it is clinically appropriate to link and integrate long-term disease-management strategies for both depression and other coexisting medical illnesses in elderly persons. Since most older people are treated for depression in the general medical sector, integrating and appropriately reimbursing long-term disease management for both depression and other coexisting medical disorders are important. Recent studies have demonstrated the effectiveness of strategies for short-term and continued treatment of depression in elderly patients in primary care settings.[3,4,6] Our data indicate that such strategies should be extended to encompass long-term maintenance treatment to prevent recurrence.

In summary, we evaluated both pharmacologic and psychotherapeutic strategies for preventing recurrence of major depression in patients 70 years of age or older and demonstrated that two years of maintenance treatment with paroxetine is effective. This observation can inform long-term disease-management strategies for the treatment of elderly patients with depression in general medical settings.

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Dr. Pollock reports having served as a member of the Paxil–Controlled-Release National Psychiatry Advisory Board and having received support from GlaxoSmithKline for laboratory research not connected with the research described in this article. Dr. Mulsant reports having received honoraria from GlaxoSmithKline. No other conflict of interest relevant to this article was reported.

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Older community residents with depression: long-term treatment with sertraline

Randomised, double-blind, placebo-controlled study

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Background Despite a growing use of selective serotonin reuptake inhibitors in older people, only one trial has examined their prophylactic efficacy in people aged 65 years and over.

Aims To examine the efficacy of sertraline in preventing the recurrence of depression in older people living in the community.

Method Participants were openly treated with sertraline and then randomised into a double-blind, placebo-controlled continuation/maintenance study of about 2 years duration. Drug dosage was maintained at levels that achieved remission.

Results No significant difference between the sertraline and placebo groups was found in the proportion of recurrences (−7.9%; 95% CI −28.06 to 12.23). Increased age and minor residual symptoms during the continuation phase were associated with recurrence.

Conclusions Sertraline at therapeutic dosage does not provide significant protection against recurrence.

Declaration of interest The study was sponsored by Pfizer Ltd.

Up to a tenth of people living in the community who are aged 65 years or more suffer from depression severe enough to warrant intervention. Just under 2% suffer from major depression (Beekman *et al*, 1999) likely to be alleviated by antidepressant therapy. Depression is associated with long-term morbidity and increased mortality (Davidson *et al*, 1988). Epidemiological studies indicate that up to 10% of older community residents with depression are treated with antidepressants. There is a growing trend in the use of selective serotonin reuptake inhibitors (Wilson *et al*, 1999), and a recent study has demonstrated efficacy of maintenance with citalopram (Klysner *et al*, 2002) in this age group. This is the first placebo-controlled trial examining the efficacy of sertraline in the prevention of recurrence of depression in older people in the community.

METHOD

Study design

The study consisted of a treatment phase (8 weeks) and a continuation phase (16–20 weeks) during which participants were treated with open-label sertraline prior to randomisation into a double-blind, parallel, placebo-controlled maintenance trial of 100 weeks. During the open phases drug dosage was titrated from 50 mg to 200 mg daily, as clinically indicated. All participants were maintained on their final therapeutic dosage (or placebo equivalent) during the randomised, controlled phase of the study, with the exception of those treated with 200 mg. In the latter cases the maintenance dosage was decreased from 200 mg to 150 mg, and each case was paired (by a third party) with a placebo recipient to maintain double-blind conditions.

Power analyses

The power of the study was initially based on recruiting 300 persons to each group. This was recalculated as the results from a similar study became available (Doogan & Caillard, 1992). This informed a new power calculation, indicating that a group size of 60 would detect a 26% difference between groups with 95% confidence and 80% power, assuming a 50% relapse/recurrence rate in the placebo group. This would also enable detection of relative risk for relapse of 0.5 for sertraline compared with placebo.

Inclusion and exclusion criteria

All participants were aged 65 years or more. Psychiatric diagnoses were established by a trained psychiatrist using criteria including Geriatric Mental State AGECAT depression level 3 or over (Copeland *et al*, 1988), DSM–III–R diagnoses of major depressive disorder (American Psychiatric Association, 1987) and a Hamilton Rating Scale for Depression (HRSD) 17-item score of 18 or over (Bech *et al*, 1981). Exclusion criteria were a Mini-Mental State Examination (MMSE) score (Folstein *et al*, 1975) of 11 or under to exclude people with severe cognitive dysfunction; severe and unstable physical illness; clinically significant alcohol misuse; significant suicidal or delusional experiences; and concomitant drug treatment, including other psychotropic drugs, warfarin and anticonvulsants.

Randomisation, allocation concealment and compliance

A company independent of the sponsor and trialist was responsible for packaging the trial drugs and randomisation. A computer-generated randomisation list was provided by Pfizer Ltd. The list was stratified by dosage and used to produce numbered containers for the identical capsules of either sertraline or placebo. Participants eligible for the maintenance phase were allocated to the next number at their dose level. Codes were maintained in opaque, sealed envelopes. They were broken on trial completion, after locking the study database. External research auditors maintained the security of the codes, and verified data collection and cleaning. Drug compliance was monitored through tablet counting at each assessment and asking the patient if any doses were missed.

Sample recruitment

Participants were recruited from the screening of all patients over 65 years of age at a

multi-partner general practice, and referrals from: a community survey conducted at the same time as the trial; twenty general practices in Liverpool; and four old age psychiatry teams.

Assessments and interviews

A trained psychiatrist conducted the initial, end-of-phase and final assessments, including DSM–III–R criteria and final HRSD scores. Initial assessment included research diagnostic and entry criteria, a physical examination and laboratory investigations, comprising blood count, vitamin B_{12} and folate measurements, and thyroid and liver function tests. Research staff conducted follow-up assessments. Staff undertook regular training and instrument standardisation throughout the study. Subsidiary instruments included the Montgomery and Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) and the Burvill Physical Health Scale (Burvill *et al*, 1990). Domiciliary interviews were conducted fortnightly during the first two phases of the study, monthly for the first 6 months of the maintenance phase and subsequently every 2 months. All participants entered into the maintenance phase were followed up, including those subsequently withdrawn from the trial.

Outcomes

Entry into the continuation phase required a 50% reduction in baseline HRSD score by 8 weeks. An HRSD score of 10 or less had to be maintained for a period of 4 weeks during the continuation phase prior to randomisation into the double-blind, placebo-controlled maintenance phase of the study. The continuation phase could be extended up to 20 weeks, depending on assessment scores. Recurrence during the maintenance phase was defined as an HRSD score of 13 or over as well as meeting DSM–III–R criteria for major depressive disorder as determined by a trained psychiatrist.

Analysis

Analysis was carried out independently of the funding body. The initial analysis compared clinical and demographic characteristics of the experimental sample with individuals withdrawn or excluded from the study before the maintenance phase. Follow-up data are provided for participants subsequently excluded because of recurrence during the maintenance phase. In the main analysis, primary outcome variables were subjected to survival analyses using Kaplan–Meier and hazard ratio calculations. The distribution of rate of recurrence across the maintenance phase is described. A Cox proportional hazards regression model was used to explore the potential influence of baseline and experimental variables in determining outcome.

Ethical approval

The study was granted ethical approval by the local ethics committee. Each participant was provided with written and verbal information. Informed consent was required prior to trial inclusion. Primary care physicians were informed of the trial and provided with a full psychiatric assessment, care programme and regular updates concerning clinical progress, for each participant.

RESULTS

Study sample

Three hundred and eighteen persons fulfilled the depression entry criteria. They had a mean age of 77.7 years (s.d.=7.1) and a mean HRSD score of 20.4 (s.d.=3.2). Sixty-four persons were subsequently excluded from entry into the treatment phase of the trial: 28 refused consent, 9 were excluded because of severe, unstable physical illness, 7 took contraindicated drugs, 1 had had a previous adverse reaction to sertraline and 6 were excluded because of protocol violations; the reasons for 13 exclusions were unrecorded. The study population (those taking at least one dose of sertraline and receiving at least one follow-up visit) consisted of 254 persons (65 men and 189 women) with a mean age of 77.6 years (s.d.=6.6). Of these, 141 failed to meet the entry criteria for the maintenance phase (Fig. 1). The remaining 113 participants were randomised to

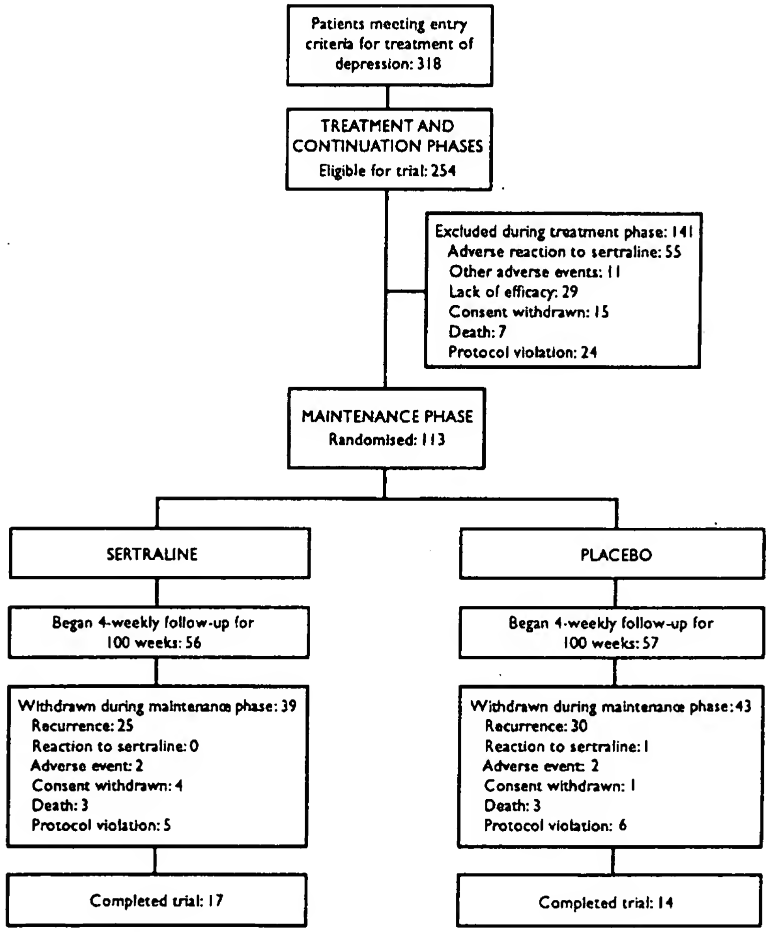

Fig. 1 Study profile.

Table 1 Demographic and baseline clinical characteristics of study participants entering analyses (double-blind, placebo-controlled maintenance phase); *n*=113

	Treatment group (*n*=56)	Control group (*n*=57)
Age (years)		
Mean (s.d.)	76.6 (6.6)	76.8 (7.0)
25th percentile	71	70.5
Median	76	77
75th percentile	83	82.5
Gender (*n*)		
Male	19	14
Female	37	43
HRSD score: mean (s.d.)	20.7 (3.7)	20.3 (3.3)
MADRS score: mean (s.d.)	26.48 (6.5)	26.0 (5.4)
BPHS score: mean (s.d.)		
Severity: acute	0.1 (0.3)	0.2 (0.7)
Severity: chronic	2.97 (2.1)	2.7 (1.8)
Disability: acute	0.13 (0.3)	0.2 (0.6)
Disability: chronic	2.58 (2.1)	2.5 (2.0)
First episode of depression (%)	71.4	73.6
Duration of episode (weeks)		
Mean (s.d.)	23.6 (29.4)	24.4 (52.1)
25th percentile	6	6
Median	12	12
75th percentile	36	24
MMSE score (out of 35): mean (s.d.)	31.1 (4.7)	30.4 (4.6)

BPHS, Burvill Physical Health Scale; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery & Åsberg Depression Rating Scale; MMSE, Mini-Mental State Examination.

receive sertraline (*n*=56) or placebo (*n*=57; Table 1). Recruitment source did not predict likelihood of entry into the maintenance phase (Pearson χ^2=3.0, d.f.=3, *P*=0.4). However, those not meeting maintenance phase entry criteria had significantly higher baseline HRSD scores (2.42, 95% CI 1.10–3.74).

Of those who were withdrawn during the maintenance phase, 84 consented to open follow-up. These included people experiencing recurrence and protocol violations. Two-thirds of this group (*n*=57) accepted subsequent antidepressant therapy of at least 8 weeks duration: 12 (21%) achieved remission (MADRS score of 6 or less), 19 (33%) remained depressed, and the remaining 26 (46%) had varying levels of improvement. Seventeen (20%) of the 84 died prior to the end of the follow-up period of 2 years.

Trial drug dosage and medication compliance

Tablets were delivered to the participants' homes, and tablet counts were conducted at each assessment. Participants were maintained on the dosage that achieved remission of presenting episode: 73% of the sertraline group and 75% of the placebo group received 50 mg daily, while the others received 100 mg daily. None received 150 mg (or placebo equivalent) during the maintenance phase.

Table 2 Cumulative recurrence[1] of depressive disorder during the 2-year maintenance phase

Week	Sertraline Total *n* randomised=56			Placebo Total *n* randomised=57		
	Patients under observation (*n*)	Cumulative recurrences (*n*)	Cumulative survival[1] (%)	Patients under observation (*n*)	Cumulative recurrences (*n*)	Cumulative survival[1] (%)
4	54	2	96.43	51	6	89.47
8	46	8	85.30	42	11	80.63
12	45	9	83.45	42	11	80.63
48	28	19	63.09	20	26	49.00
100	15	25	38.64	12	31	31.10

1. Estimated difference in proportion of participants experiencing recurrence: −7.9% (95% CI −28.06 to 12.2%).
2. Based on Kaplan–Meier estimates.

Analysis of recurrence

Kaplan–Meier survival analyses showed no significant difference (log rank test 1.55, d.f.=1, *P*=0.21) between sertraline and placebo in prevention of recurrence. The sertraline group had a cumulative survival function of 39% with a median survival of 92 weeks. The placebo group had a cumulative survival function of 31% with a median survival of 48 weeks (Table 2). There was a reduction in risk of recurrence of 8.4% over 100 weeks for people taking sertraline compared with those taking placebo during the maintenance phase.

Over half of those experiencing recurrence did so during the first 26 weeks of the maintenance phase: 15 (60%) in the placebo group, 16 (57%) in the sertraline group. Approximately a quarter (32% placebo and 16% sertraline) experienced recurrence between 27 weeks and 52 weeks. The remainder experienced recurrence during the second year of follow-up. We examined the relative rate of recurrence across time, and compared the proportion of eligible participants experiencing a recurrence at each assessment. Three main 'peaks' were identified (at 15 weeks, 30 weeks and 50 weeks) at which 8% or more of eligible participants experienced recurrence. However, at least three other peaks (at 8 weeks, 64 weeks and 72 weeks) were identified at which 5–6% of eligible participants experienced a recurrence.

Cox's regression analysis

Clinical and demographic variables were entered into a stepwise analysis (backwards

elimination) to investigate models of recurrence prediction. Eleven items were entered into the first stage of the regression. Of these, sertraline *v.* placebo, MMSE score, length of presenting episode, previous number of episodes, Burvill scores (of which there are four separate sub-scores) and gender were dropped. Dosage of maintenance medication was associated with baseline severity of depression: high dosage did not protect against recurrence. Age (in 5-year increments) and pre-randomisation MADRS score were predictive of recurrence (Table 3). Each 5-year increase in age has a hazard ratio of 1.30 (95% CI 1.04–1.61). A one-point increase in pre-randomisation (end of continuation phase) MADRS score has a hazard ratio of 1.11 (95% CI 1.02–1.20) for recurrence.

DISCUSSION

This is the first maintenance study to challenge the assumption that the dosage of an antidepressant that achieves remission also provides protection against recurrence. We examine our findings in terms of design limitations and in the context of contemporaneous literature.

Limitations of the study

Studies of a similar nature (Ardern *et al*, 1993) have been criticised for selection bias, excluding a large percentage of the eligible sample and not supplying information about those who were excluded or follow-up of those who experienced recurrence during the trial. We recruited participants from four different sources, reducing the likelihood of selection bias. Recruitment source did not influence eligibility to enter the maintenance phase and was not associated with outcome. In this study, relatively few people were excluded because of concomitant physical illness (*n*=9). However, analysis demonstrates that those with more severe depression were excluded from entry into the maintenance phase. Consequently, our findings reflect the prophylactic efficacy of therapeutic doses of sertraline in older people in the community who are suffering from mild to moderate severity of DSM–III–R major depressive disorder. Of those who did experience recurrence, two-thirds accepted a second antidepressant or increased dose of sertraline, of whom under a quarter had a good outcome, while the remainder showed some improvement. However, the mortality rate over 2 years was high in this group.

The design of this study may be criticised because of its relatively short continuation phase. Guidelines suggest that the continuation phase should be up to 6 months' duration, based on the assumption that a depressive episode lasts 6–9 months in those treated as out-patients (Kupfer & Frank, 1992). However, as in the study by Klysner *et al* (2002), there was no significant peak of recurrence within the first few months of the maintenance phase in the placebo group, as would be expected if participants were experiencing relapse as opposed to recurrence.

Table 3 Cox regression model predicting recurrence

	Hazard ratio	95% CI
Included variables		
Sertraline v. placebo	1.21	0.704–2.082
MADRS score at end of phase 2	1.11	1.019–1.200
Age (5-year increments)	1.30	1.044–1.613
Rejected variables		
Gender (male:female)	0.95	0.52–1.73
Length of episode	1.00	1.0–1.01
Previous episodes	1.01	0.89–1.14
MMSE score	0.93	0.93–1.04
BPHS score:		
Severity: acute	1.00	0.58–1.46
Severity: chronic	0.89	0.89–1.15
Disability: acute	0.90	0.55–1.50
Disability: chronic	1.01	0.93–1.18

BPHS, Burvill Physical Health Scale; MADRS, Montgomery & Åsberg Depression Rating Scale; MMSE, Mini-Mental State Examination.

The study may also be criticised on the grounds of potential type II error. The power analysis indicated that 60 participants should be recruited into each arm of the post-randomisation phase. Owing to protocol violations identified after recruitment was closed, 6 persons (0.05% of the study sample) were subsequently excluded from the analyses. Statistical modelling indicated that the inclusion of these individuals in the appropriate experimental arms and allocating them to the outcome that favours drug efficacy compared with placebo did not significantly influence the results. Our study is comparable in size to that of Klysner *et al* (2002), which was of a similar design, evaluating an antidepressant from the same class. Other studies in this age group that are of similar design are approximately half the size of our study. Ardern *et al* (1993) studied 58 persons, 25 of whom received dothiepin and 35 received placebo; Reynolds *et al* (1999) studied 53 persons (excluding those receiving psychotherapy), of whom 24 received nortriptyline and the remainder received placebo. Despite being of similar size to our study or smaller, all three studies (Ardern *et al*, 1993; Reynolds *et al*, 1999; Klysner *et al*, 2002) found in favour of antidepressant treatment compared with placebo.

Other potential criticisms lie in the possibility of poor compliance and the use of relatively low dosages of sertraline in a proportion of participants. Reynolds *et al* (1999) demonstrated the prophylactic efficacy of therapeutic levels of nortriptyline. Poor compliance and sub-therapeutic blood levels are thought to explain up to 50% of the recurrence in that study. The authors also suggest that sub-therapeutic blood levels explain the negative findings of other, smaller studies (Georgotas *et al*, 1989) examining the prophylactic efficacy of the same drug. In a small study examining the efficacy of lithium and cognitive–behavioural therapy in the prevention of recurrence and relapse, Wilson *et al* (1995) noted that poor drug compliance resulting in low serum lithium levels confounded the findings.

We believe that low dosage is unlikely to be responsible for the findings of our study. Participants were maintained on the dosage of sertraline at which they achieved remission; three-quarters took 50 mg daily, which is recognised as the optimum dose for treatment (Preskorn & Lane, 1995),

and about a quarter were treated with 100 mg. High dosage was associated with increased severity of index depression and did not have an increased protective effect in terms of outcome. Compliance is more difficult to monitor. Compliance was enhanced through domiciliary delivery of medication and supportive, ongoing counselling, emphasising the importance of medication, with tablet counting at each assessment. Analysis failed to demonstrate any difference between tablet returns in those experiencing recurrence compared with those who remained asymptomatic in the sertraline group. There was no difference between those who received sertraline and those who received placebo in terms of compliance monitoring. Blanchard *et al* (1999) demonstrated the importance of generic nurse support in the longer-term management of depression in older community residents. The follow-up in this study was intense, with regular home visits augmented by telephone contact. Members of both placebo and experimental groups received similar support in terms of nature and number of contacts during the experimental period. It is unlikely that differential support influenced the findings.

Our findings in context

We have found two studies that have examined the prophylactic efficacy of sertraline. Doogan & Caillard (1992) found that sertraline was more effective than placebo in preventing recurrence in 144 subjects over 44 weeks. Keller (1998) found similar results in a younger population over 76 weeks. However, the design of both these studies included a facility to increase maintenance dosage (preserving masking integrity) in people who were thought to be showing early evidence of recurrence during the double-blind, placebo-controlled phase. An analysis of presented data suggests that a significant proportion of those experiencing potential recurrence benefited from a subsequent dosage increase in each study. These findings are reflected in the 'treatment of recurrence' study by Franchini *et al* (2000), who found that increasing the dosage of sertraline had a therapeutic role in the management of recurrence in people with depression who were already taking the drug. Our study design did not have the facility of increasing maintenance dosage when early signs of recurrence became obvious; participants were maintained at the dosage of sertraline that achieved remission of the presenting episode. A subsequent search of the Cochrane Database of randomised, controlled trials failed to generate any evidence that the dosage of sertraline required to achieve remission has prophylactic efficacy and that enhanced dosage is probably required for maintenance treatment.

Predictive variables

As in our study, Reynolds *et al* (1999) found an association between increased age and recurrence. Notably, these observations are independent of the number of preceding episodes experienced by the individual. Follow-up studies of patients referred to secondary services have demonstrated a mixed association between acute and chronic physical illness and handicap (Burvill *et al*, 1991). We were unable to demonstrate any significant correlation between these variables and outcome. Again, our findings concur with those of Reynolds *et al* (1999), who examined these issues in the context of a randomised, controlled trial. Our finding that following remission, residual depressive symptoms predict poor outcome in terms of recurrence has been found in other treatment-controlled studies (Faravelli *et al*, 1986).

Clinical and research implications

A number of research issues are generated by these findings. First, there is no doubt that sertraline is a relatively safe and therapeutically active drug (Finkel *et al*, 2000) which has been examined in the context of prophylactic treatment. Despite these later studies (Keller, 1998; Finkel *et al*, 2000) being positive, our negative findings are consistent when study design is taken into account. In this study we specifically examined the prophylactic efficacy of sertraline prescribed at the dosage required to achieve remission. This differs from other studies, which clearly demonstrate the prophylactic efficacy of sertraline provided that the dosage is increased over and above that required to achieve remission of the presenting episode. These negative findings are important. It is apparent that in the absence of evidence, it cannot be assumed that the dosage of antidepressant required to achieve remission offers protection against recurrence or relapse: in the case of sertraline, the effective prophylactic dosage is likely to be greater than the therapeutic dosage. Second, in comparing this study with other studies conducted on similar populations it is evident that antidepressants differ in terms of maintenance efficacy. A review of the literature indicates that this is not a class-specific phenomenon and emphasises the importance of randomised, controlled trials in establishing prophylactic efficacy (and dosage) before new antidepressants are routinely employed in this fashion. Third, it is evident that extreme age is associated with an increased risk of recurrence of depression over 2 years – in the study by Reynolds *et al* (1999), 3 years. It is important in future that maintenance trials are developed to accommodate these issues, bearing in mind the relatively high levels of morbidity and suicide in this age group.

From a clinical perspective, three specific recommendations can be drawn from our findings. First, this study draws attention to the particular vulnerability of very old people with depression living in the community. It is evident that emphasis must be placed on maximising symptom control during the treatment phase. Even minor (sub-syndromal) residual symptoms are predictive of poor outcome in terms of recurrence. This warrants an aggressive and closely observed treatment plan. Second, it is also apparent that the very old are particularly vulnerable to recurrence. This is independent of the number of previous episodes experienced by the individual. Consequently, these people should be encouraged to take long-term maintenance medication, irrespective of the number of previous episodes. Third, it is not safe to assume (in the absence of evidence) that the therapeutically active dose of an antidepressant that promoted remission has prophylactic efficacy. Increased dosage may be required in the context of long-term, closely followed-up therapy, with counselling and compliance monitoring.

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CLINICAL IMPLICATIONS

- The sertraline dosage required to achieve remission of depression in older people does not have significant prophylactic efficacy. However, research suggests that increasing the dosage at the first sign of recurrence does have a role.
- Residual depressive symptoms after treatment are associated with recurrence, suggesting that complete symptom control should be a priority of treatment.
- Very old people are particularly vulnerable to recurrence of depression (irrespective of physical illness, handicap and number of previous episodes), suggesting that prophylactic treatment should be considered after the first episode.

LIMITATIONS

- The study findings can only be generalised to older people with mild or moderate major depressive disorder, living in the community.
- Compliance was not assessed by measuring serum drug levels.
- This is one of a very few studies reporting that the dosage of an antidepressant required to achieve remission does not have prophylactic efficacy. Replication studies and meta-analysis are required to confirm the findings.

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LOADING DOSE IMIPRAMINE—NEW APPROACH TO PHARMACOTHERAPY OF MELANCHOLIC DEPRESSION

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Summary—This study investigated the therapeutic efficacy of loading doses of imipramine hydrochloride and compared it with that of conventional gradually escalating dose regimen of the same drug in 16 melancholic depressives (DSM III-R), done in a comparative, randomized, double-blind research design. There were four males and four females in each group who were comparable on socio-demographic and clinical variables. The study group received the bolus doses of imipramine on two consecutive days and was free of any antidepressant treatment between day 3 and day 7 of the treatment period, whereas the control group received the conventional regime of gradual escalation of imipramine dose over a period of 7 days. The results indicate that imipramine hydrochloride can relieve depression almost completely within 72 h, if given in high bolus doses, thus challenging the theory of lag period for antidepressant action as an inherent property of this drug. The study shows that the pulse loading dose was superior to a conventional dose regime with regard to both antidepressant efficacy and rapidity of onset of action. The various mechanisms possibly involved in such a dramatic improvement and its implications have been discussed.

Introduction

Since the discovery of imipramine hydrochloride as an antidepressant agent almost three decades ago, it has continued to remain as the standard and most effective treatment for depression. However, the greatest disadvantage of imipramine, and also of other tricyclic antidepressants (TCAs), has been the variable lag period before therapeutic response manifests. Though sedative and anxiolytic effects start quite early following the institution of TCAs, the "core" symptoms of depression such as sad mood, cognitive changes and psychomotor retardation often take 2–3 weeks to improve (Hippius & Winokur, 1983).

There are various theories to explain the "lag period". It has been hypothesized that TCAs basically act by inhibiting the re-uptake of norepinephrine and serotonin, and that it takes 2–3 weeks for the transmitter amines to migrate down the axon to nerve endings where they become active (Dunleowy et al., 1972). However, most studies have demonstrated that acute effects on metabolism and uptake manifest within hours or days, and the protracted course of action was difficult to reconcile with this fact. Repeated administration of TCAs have also been shown to enhance the presynaptic and postsynaptic receptor density and sensitivity, which parallel the time course of clinical action and could

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account for the gap between institution of drugs and onset of its therapeutic action (Kaplan & Sadock, 1989). A combination of re-uptake and receptor mechanisms, e.g. increase in transmitters in the synaptic cleft resulting in presynaptic receptor down-regulation, has been considered (Siever et al., 1981). More recently, it has been suggested that TCAs act through synchronization of circadian rhythms, which again takes about 2–3 weeks to achieve (Healy, 1989).

The pathophysiological CNS changes in depression appear to consist of presynaptic alterations in neurotransmitter synthesis, release, metabolism and/or uptake, as well as postsynaptic receptor, transducer (G-protein), second messenger (cyclases and the phosphatidylinositol system) and/or ion transport irregularities (Racagni et al., 1991). The presynaptic changes probably reflect the acute actions of antidepressants while the postsynaptic changes are correlated with the chronic adaptive responses that coincide with the onset of the therapeutic effect (Racagni et al., 1991). As all antidepressants have a 2–3 week onset of action (Aberg-Wistedt, 1989), their antidepressant efficacy seems to be attributable to presynaptic neuroadaptive changes (e.g. in the G-protein); presynaptic changes may simply serve as an acute trigger for long-term activity (Racagni et al., 1991).

However, a more simple explanation could involve the pharmacokinetic processes such as extensive hepatic clearance and protein binding of the TCA. Lefur (1980) found that steady-state levels of imipramine in the brain were reached within 2 weeks of administration of the drug, thus correlating with onset of clinical efficacy. Pharmacokinetic factors such as bioavailability could also act via pharmacodynamic mechanisms. Sethy et al. (1983) have demonstrated that β down-regulation, one of the frequently cited causes of latency in antidepressant response, is to a considerable extent influenced by the quantity of TCA initially administered.

Whatever the mechanism, this latency in onset of substantial or maximal change often has significant clinical implications. As a result of this gap in onset of mood elevation, some patients become discouraged and stop treatment too soon, especially those who have not been informed about the pattern of clinical response (Hollister, 1983). The initial improvement in sleep is often misleading, since it is not usually predictive of subsequent treatment outcome. It is often difficult to decide whether the patient will respond to a particular drug and this decision cannot be reached before 4–6 weeks (Kaplan & Sadock, 1989). Most significantly, the delay in onset of clinical efficacy limits the usefulness of these drugs in cases with a high risk of suicide or severe depression, where electroconvulsive therapy is usually preferred.

However, some recent studies have shown that it is possible to achieve a more rapid onset of antidepressant response with loading doses of either oral or parenteral antidepressants (Pollock et al., 1989). In our clinical experience we observed in two patients with depression, who had recovered from an overdose of imipramine hydrochloride (approximately 250–300 mg) which they had taken in order to commit suicide, a total disappearance of depression symptoms within 2–3 days of the ingestion of the drug. This remarkable clinical observation supported the above hypothesis and stimulated our interest in studying this phenomenon.

The importance of initial dosages of antidepressants, with regard to rate and extent of therapeutic response, has largely remained unexamined. Hirschowitz et al. (1985) reported that desimipramine when started at 200 mg/day right at the beginning, produced sig-

nificantly greater improvement than the control group receiving conventional escalating dosage regime. Pollock et al. (1986) studied the effects of two pulse loading doses of intravenous clomipramine administered to 10 patients over a 24-h period. Eight of these patients showed improvement compared with a control group of four patients, none of whom showed improvement when given isotonic saline solution.

Pollock et al. (1989) in another trial, reported a double-blind trial of oral vs intravenous pulse loading doses of clomipramine. A significant reduction in depressive symptoms was noted in 5 days following the pulse doses. No significant differences were noted between the oral and intravenous groups with regard to either efficacy or side-effects.

Thus its seems that pulse loading (defined as rapid attainment of optimal initial bioavailability) dose regimens can lead to a faster and probably better therapeutic response than conventional dosage regimens, involving gradual escalation.

This study was planned to investigate the efficacy of an oral pulse loading dose regimen of imipramine hydrochloride in a double-blind, randomized and controlled trial.

Aims and objectives

The main aim was to study therapeutic efficacy of loading doses of imipramine hydrochloride and to compare it with that of a conventional, gradually escalating dose regimen of the same drug in patients with melancholic depression.

Materials and methods

The sample was chosen from a population of patients attending the psychiatry outpatient clinic of the Department of Psychiatry, Nehru Hospital, Postgraduate Institute of Medical Education and Research, Chandigarh. This project had obtained a clearance from the Ethics Committee of the Institute.

The patients aged between 15 and 60 years, and with DSM III-R (APA, 1987) diagnosis of major depression with a single or recurrent episode with melancholia, were included. Those who had other concomitant Axis I diagnosis (e.g. dysthymia, substance abuse or organicity), or psychotic features, were excluded. Informed consent was taken from all subjects before they entered the study.

None of the recruited patients were on any psychotropic medication at the time of and 2 weeks prior to inclusion into the study. All patients had, at least, a minimum score of 22 on the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) at intake. These patients were randomly allocated to the two groups, namely, the loading dose (experimental) group and the conventional dose (control) group. All patients were admitted to hospital for at least the entire duration of the study.

Patients in the experimental group were administered with 225 mg of imipramine hydrochloride at 7:00 p.m. for the first two consecutive days. They received similar-looking placebo tablets between the third and seventh day. From the eighth day to the 21st day, patients in this group received a standard dose of 150 mg/day in divided doses (75 mg b.d.). The control group received a single evening dose of imipramine 75 mg per day for the first 2 days and 100 mg/day from the third to fifth day, 125 mg/day on the sixth and seventh day and 150 mg/day from the eighth day onwards. Thus, both groups received 150 mg

imipramine/day from the eighth day to the 21st day. Patients in both groups received the same number of similar-looking tablets administered by the first author (SM) who alone knew the actual dose of imipramine being given. There was no concomitant medication given. The trial was terminated after this. However, a detailed follow-up of the patient was done at the end of 1 and 3 months after start of treatment.

The following assessments were done before the start of therapy and at different times during the course of treatment on the following parameters.

1. Rating of depression on the 21-item Hamilton Depression Rating Scale (HDRS) and Melancholia Evaluation Scale (MES) before the start of therapy and every 3 days (Hamilton, 1960; Bech & Rafaelsen, 1980).
2. Assessment of side-effects using the check list, every 3 days. A detailed physical examination was done daily during the first week of administration and repeated whenever necessary thereafter.
3. An electrocardiogram was done twice in the first week and once a week thereafter (more frequently if needed).
4. Haemogram, serum electrolytes, renal function tests and liver function tests were done weekly.

The ratings were done by the second author (PJS) who was blind to the doses of imipramine being received by patients.

It was decided to drop any patients from the study if he/she developed any serious physical complication, serious side-effects or the clinical condition warranted additional treatment such as antipsychotics or ECTs, or if the patient decided to opt-out or seek early discharge from the ward.

Results

Sixteen inpatients entered the study, none of whom dropped out. The two groups each consisted of four males and four females. The mean age of the experimental group was 38.3 ± 8.24 years, and that of the control group 41.5 ± 11.54 years. The two groups did not differ in education, occupation, income or locality of stay, the mean duration of current episode which was 6.9 ± 4.26 months in the experimental group and 7.1 ± 5.12 months in the control group. There was no difference in the number of previous depressive episodes in the two groups which ranged between 0 and 3 for all patients. The HDRS scores (mean ± *SD*) on the day of starting treatment were 28.38 ± 5.21 and 27.5 ± 4 in the experimental and control groups, respectively. MES score was 12.75 ± 2.12 and 12.00 ± 1.85 in the two groups, respectively. On the third day after pulse loading, the HDRS mean ± *SD* for the experimental group had dropped to 12.25 ± 6.36 whereas for the control group receiving 75 mg/day, it had only decreased to 26.75 ± 3.85 (Table 1). The mean improvement on day 3, for the experimental group was highly significant (paired t-test $= 5.97$, $df = 7$, $p < .001$) relative to the day 0 rating. It is evident from Figure 1 that significant improvement occurred in seven of the eight patients in the experimental group. They had improved even in the core melancholic symptoms (rated on MES) within the first 3 days, while none of the patients in the control group showed any improvement. One patient did not improve in the

Table 1
Mean Differences in Hamilton Depression Rating Scale (HDRS) Scores over Time in the Two Groups

Day	Experimental group		Control group	
	$n=8$	$n=8$	t value	p value
0	28.38±5.21	27.50±4.00	1.17	ns
3	12.25±6.36	26.75±3.85	−5.16	<.001
7	6.15±7.22	25.87±3.64	−6.46	<.001
14	3.25±6.11	24.50±3.34	−8.08	<.001
21	1.25±8.9	22.75±3.06	−6.06	<.001

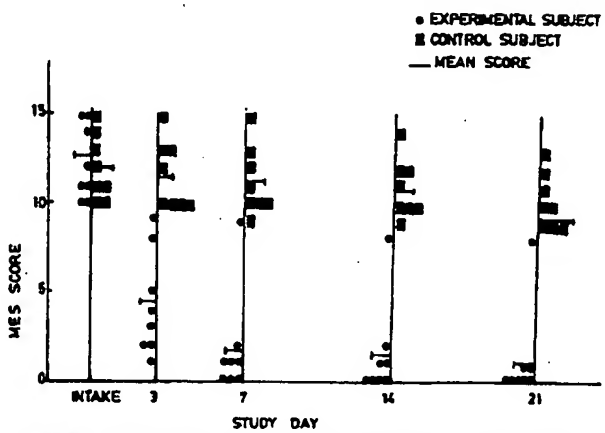

Figure 1. Differences in MES scores over time in the two groups.

experimental group and on reviewing the history of this patient, it came to light that in her earlier episode, she had not responded to 225 mg/day of imipramine given for 10 weeks and had improved only marginally with ECTs. This patient was switched to ECTs from the day of termination of the trial and she showed only a marginal improvement (40%) in her depression even after eight ECTs. Subsequently, a combination of antipsychotics and antidepressants effected recovery in her after 3 months.

All the seven patients who had improved with the loading dosage schedule persisted with their improvement even at 3 months after the therapy.

Adverse effects experienced by the patients in the two groups are given in Table 2. The patient tolerance of the loading procedure was good, and there were no significant adverse reactions. Only one patient in the experimental group developed abdominal discomfort and distention with sluggish bowel sounds, which was treated conservatively, and the patient recovered within 24 h. It was noted that side-effects appeared faster in the experimental group, as opposed to the control group. The side-effects were not significant enough for the patients to consider stopping medication in either of the groups.

Table 2
Percentage of Patients Experiencing Side-effects over Time in the Two Groups

		Experimental group (*n*=8)(%)					Control group (*n*=8)(%)				
Sl. No.	Side-effect	Day 1	Day 3	Day 7	Day 14	Day 21	Day 1	Day 3	Day 7	Day 14	Day 21
1	Dry mouth	100	87.5	62.5	25	0	25	37.5	50.0	62.5	50.0
2	Sedation	25.0	12.5	0	0	0	0	0	12.5	12.5	0
3	Giddiness	37.5	12.5	0	0	0	12.5	12.5	37.5	25.0	0
4	Constipation	62.5	62.5	12.5	0	0	0	25.0	62.5	62.5	37.5
5	Blurring of vision	37.5	25.0	0	0	0	0	0	12.5	12.5	0
6	Tremor	37.5	25.0	0	0	0	0	0	25.0	37.5	12.5
7	Postural hypotension	12.5	12.5	0	0	0	0	0	12.5	12.5	12.5
8	Abdominal discomfort	0	0	12.5	0	0	0	0	0	0	0

Discussion

The results of this exploratory descriptive study clearly indicate that imipramine hydrochloride can relieve depression almost totally, within 72 h if given in high bolus doses, thus challenging the theory of a lag period of antidepressant action as an inherent property of this drug.

All of the patients except one in the experimental group felt such a remarkable change in the feeling state by the third day of treatment that many of them remarked it felt "as if a veil has lifted and they see the brightness of the day". This initial improvement continued for 7 days without any other drug and was maintained until the end of 3 months with a standard dose of 150 mg/day of imipramine started from the eighth day onwards. It is remarkable that seven out of eight patients achieved full remission at the end of 7 days in the study group, but the treatment was ineffective in the control group even after 21 days of treatment. It is possible that the rate of improvement was slower in the control group, or that these patients needed a higher dose of imipramine than 150 mg/day. In fact, one cannot be sure how long the improvement would have lasted after the initial loading dose, which is a research question which should be examined and further studied. Moreover, it was seen that the tolerance and acceptability of such a dose regimen in patients was very high. We were very cautious in using this high loading dose of imipramine, particularly because of the risk of cardiac and CNS toxicity, and all patients were admitted to hospital for this reason. There were no serious side-effects encountered warranting discontinuation of therapy and none of the patients showed any cardiotoxicity, which is one of the major reasons why slow dose regimens are advocated for imipramine and other tricyclic antidepressants. In addition, the side-effects were more marked in the initial phase of treatment in the study group, in the study group the overall side-effects were much fewer and milder at the end of 21 days compared with the control group. It may be a result of the fact that the total amount of imipramine received by the control group in the first 7 days of treatment which was much higher (700 mg) than that received by the study group (450 mg) in the corresponding period. Although, this work is of preliminary nature it provides some evidence for the validity of findings which need to be studied further.

This study is the first of its kind using imipramine in two dosage schedules, oral pulse

loading and gradually escalated dose regimen, done in a comparative, randomized, double-blind research design. The findings therefore, remain uncomparable. Studies by Hirschowitz et al. (1985) and Pollock et al. (1989) are further supported by our results and substantiate the hypothesis that pharmacokinetic processes may be crucial to therapeutic response.

Stassen et al. (1993) reported that time-course of improvement with antidepressant treatment was dependent upon the initial triggering of recovery rather than on the type of drug used. Once a drug response is initiated the subsequent course of recovery from illness is independent of the drug used.

Different effects may be observed at the same concentration of a drug as a consequence of time-dependent events, such as equilibration delay, formation of active metabolites or changes in receptor density (Holford & Sheiner, 1981). Thus, a pulse-loading regime could probably act at any of these levels to produce a sustained improvement in depression. Postsynaptic β-receptor down-regulation has been reported to correlate with antidepressant response. Sethy et al. (1983) reported that the time of onset of down-regulation of β-receptors was negatively correlated with the doses of TCA and that this down-regulation may mediate the therapeutic effects of antidepressants. This could imply that pulse-loading regimes may induce a quick and stable β-receptor down-regulation which could explain the superior antidepressant activity found in our study. Another explanation could be that loading doses induce presynaptic changes which are capable of triggering an early and sustained postsynaptic change (e.g. changes in G-protein or cyclase), which results in the disappearence of depression.

Chronopharmacology is the study of how the effects of drugs vary with biological timing and endogenous periodicities. Chronotherapy is the use of a chronopharmacological approach to clinical treatment so as to enhance both effectiveness and tolerance of a drug by determining the best biological timing for its dosing (Reinberg, 1992). It could be hypothesized that since melancholic depressives are known to have disturbed biorhythms, the dosing schedule of 225 mg imipramine given at 7:00 p.m. may have been the ideal time for therapy as per chronotherapeutic principles, and has hence produced this phenomenonal antidepressant effect in the experimental group. This hypothesis will need to be validated using similar high dosing schedules at different times of the day.

The major lacunae of the present study is the absence of evaluation of corresponding blood levels of imipramine hydrochloride and its metabolites during the study period, which was not possible owing to the lack of standardized estimations for the drug at our laboratory. It is possible that due to a small sample size random allocation of patients may have led to the inclusion of "neurobiologically different" patients in both groups.

Despite the small number of patients in this study, the robust differences in therapeutic response between the groups make us optimistic that similar findings will emerge when replicated on a larger sample. There is need for caution in using loading doses of tricyclic antidepressant because of the potential risk of serious toxic effects, such as seizures, delirium or cardiac arrhythmias, particularly among slow metabolizers.

The importance of this study lies in opening the frontiers of a new psychopharmacotherapeutic approach, i.e. pulse-loading, as a viable option to the standard, gradually increasing dosage regime for antidepressants. This could result in faster antidepressant activity, with no greater risk of side-effects and, ultimately, may help us understand the

basic biological basis of depression. Currently, different regimes of pulse-loading are being tried out in our department and specific guidelines regarding the duration of antidepressant therapy after an initial pulse-loading are being worked out. This approach to therapy could help drastically decrease the total dosage of antidepressants in melancholic depression which could prove a more cost-effective option than the conventional regimes. Future studies should involve larger numbers, use estimations of blood levels of the drug and assess biological parameters of receptor functioning in order to understand this important phenomenon.

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Recurrent brief depression in general practice

Clinical features, comorbidity with other disorders, and need for treatment

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Abstract This study tested the clinical validity of the new diagnostic entity "recurrent brief depression" (RBD) in 300 general practice patients who participated in the WHO study on "Psychological Problems in Primary Care." Patients with current RBD reported episodes major depression more often than did a comparison group of nondepressed general practice patients: however, the majority of RBD patients had not received a diagnostic of any well-established affective disorder during the last 12 months. RBD patients (without MDE) did not suffer more frequently from dysthymia, from nonaffective psychiatric disorders, or from somatic disorders. However, RBD was associated with a higher percentage of previous suicide attempts and of ideation of suicide and death. RBD was accompanied by substantial psychosocial impairment; psychosocial impairment in RBD patients could not be explained by excess comorbidity. Thus, the clinical validity of RBD was demonstrated although doubts about the appropriateness of the definition remained. This new diagnostic category needs more attention as only a small minority of patients with RBD received specific antidepressant treatment.

Key words Recurrent brief depression · Major depression · Subthreshold depression · Suicide Comorbidity · Antidepressant treatment · General practice

Introduction

Community and primary care surveys have identified substantial proportions of subjects who are suffering from depressive symptoms and who are in need for antidepressant treatment, but do not fulfill the criteria for the well-defined categories of depressive disorders (such as major depression and dysthymia) (Angst 1988). Operational criteria for depressive disorders in diagnostic manuals are designed in this restrictive manner in order to avoid the allocation of diagnoses to subjects who are not suffering from depression or who are not in need of somatic or psychological treatment. The Zurich Study explored the pattern of complaints among subjects reporting to suffer from and be treated for depression, but who are not allocated to a DSM-III diagnosis of affective disorders: Cross sectionally, these subjects reported a similar number of symptoms as is usually associated with major depression, but failed to fulfill the criterion of a continuing duration of the disorder of at least 2 weeks. Substantial impairment and treatment-seeking behavior emerged mainly from the highly recurrent nature of these brief episodes of depression. A similar proportion of treated cases of RBD and of treated cases of MDE was observed in the general population (altogether more than 70% of all cases treated for depression) (Angst et al. 1993). In both groups, a substantial proportion of cases received treatment by the general practitioners.

The validity of the RBD diagnosis was furthermore supported by clinical studies: Montgomery et al. (1989, 1990) reported an increased risk of suicide attempts among RBD patients in a psychiatric outpatient clinic; Staner et al. (1992) found RBD to be located between MDE patients and controls with regard to biological indicators of depression. However, despite this body of evidence, the concept of RBD has not been generally accepted (e.g. the task force on DSM-IV, APA 1993). One reason for the reluctance to include RBD as a regular diagnostic category in DSM-IV might be that patients with RBD are usually not treated by psychiatrists, but by general practitioners. Therefore, primary care settings provide the ideal setting for exploring the validity of this new diagnostic category. The WHO study on "Psychological Problems in Primary Care" is a most ambitious study in this field (Sartorius et al. 1993). In our participating center, this study was extended by an investigation of the validity of RBD.

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The goal of this paper is to evaluate the clinical validity of recurrent brief depression in terms of clinical features, psychosocial impairment, and comorbidity with other psychiatric and somatic syndromes. Patients with RBD are compared to patients with major depression and to patients without depression with regard to these features. As is demonstrated in another paper from this study (Maier et al. 1994), a considerable proportion of primary care patients report highly recurrent brief episodes of depression which fail to fulfil the stringent definition proposed by Angst et al. (1990). The clinical features of these fringe cases were also explored in order to clarify the distinctness of the boundaries of the diagnostic definition of RBD.

Methods

Sampling of patients and assessment tools

Sampling of patients is extensively described in an adjoining report (Maier et al. 1994). Diagnostic classifications of psychiatric disorders in the sample under study were based on the CIDI interview and on a supplementary interview focusing on the phenomenology and course of brief episodes of mood disturbances and other complaints usually associated with affective disorders: These tools and the mode of their application were also extensively described in the adjoining report. The diagnoses in this report refer to DSM-III-R. RBD is defined as proposed by Angst et al. (1990). Subthreshold RBD is defined by multiple occurrence of brief episodes of depression (i.e. duration per episode lasting no longer than 2 weeks), cross sectionally fulfilling DSM-III-R criteria for DSM-III-R occurring at least once monthly during a 6-month interval, but not fulfilling RBD criteria. All prevalence rates for diagnoses in this report refer to the last 12 months (if not explicitly stated otherwise).

Somatic syndromes were identified by the treating physician in a free manner on a physician's encounter form. These diagnoses were transfered to ICD-10 codes. The presence of multiple syndromes could also be rated. This report uses the most frequently occurring somatic syndromes for the analysis of comorbidity. A list of treatment strategies and prescribed drugs was also completed by the general practitioner. The patient reported his or her reasons for contacting the physician in an unstructured manner; several reasons could be mentioned, but the patient was also asked for a single main reason. The answers of the patients were transferred by the study investigator to a preestablished list of 28 reasons

Social disability was examined by a semistructured interview (Social Disability Schedule, Wiersma et al. 1990). This schedule advises the interviewer to score four subscales measuring level of performance in four different areas of functioning (among them, adjustment to daily routine, energy input and performance, and contact with other people at work): Four scores per dimension were defined between 0 (no disability) and 3 (severe disability). In addition, a global disability score indicates the maximum level of social impairment in any of the areas of functioning.

Functioning in social roles was also used for comparing groups of patients. This dimension was extracted from the Brief Disability Questionnaire (BDQ), a self rating questionnaire developed by the WHO. A substantial proportion of patients were without work; therefore, we prefered this measure of deterioration of social relations to other measures, as it does not differentiate between private and professional life. This item is defined by four scores between 0 (no deterioration) and 3 (severe deterioration). The patient is also requested on the BDQ to estimate the number of days during the last month he or she was unable to fully carry out usual daily activities. This estimate was selected as a criterion as well.

Analytic Methods

Prevalences of disorders and frequency of scores in the various comparison groups were calculated as weighted means. Each group member was weighted by the sex-specific weight of the stratum the patient belonged to.

Two statistical strategies were applied for the analysis of comorbidity:

1. Odds ratios, currently the most widely accepted indicator excess comorbidity. Mean odds ratios are not dependent on sample size, as are other measures of association. Confidence intervals can be estimated as proposed by Agresti (1990). An odds ratio of 1,0 indicates concurrence of disorders just by chance; higher values indicate less concurrence than would be expected by chance. Odds ratios refer to the total sample; they reflect concurrence between two diagnostic entities and cannot be controlled for additional occurrence of a third diagnostic entity.

2. Mediation of excess concurrence between two disorders by a third diagnostic group. In particular, excess concurrence between RBD and a nonaffective psychiatric disorder may be due to the excess concurrence of MDE with both of them. In order to rule out that an association between RBD and another disorder detected by odds ratios is mediated by MDE, we compared patients with RBD but without MDE or dysthymia to patients without any current syndrome of depression (i.e. without MDE, dysthymia, RBD or subthreshold RBD) by a chi-square statistic.

Other statistical tests applied were *t*-tests for testing for equality between means of continuous variables, and chi-square tests for testing for equality of the distribution of categorial variables between two comparison groups.

Studies exploring the validity of a diagnostic group should determine a priori the sample size of the comparison groups under study in order to control for statistical errors. The design of this study did not allow for this procedure; the size of the sample of all general practice patients was fixed rather than the sample size of subgroups. The number of patients receiving RBD diagnosis were limited ($n = 19$ and 10, see Table 1). Thus, all comparisons between RBD patients and nondepressed patients are overconservative. However, this limitation does not introduce a bias in favor of the validity of RBD.

Results

Sample under study

Among the stratified sample of 300 patients (Table 1) were identified 55 cases with an episode of major depression during the last 12 months, 2 cases with current dysthymia, 29 cases with current recurrent brief depression, and 67 cases with subthreshold recurrent brief depression during the last 12 months. Recurrent brief depression and major depression coincide in the same subjects during the last 12 months significantly more frequently than would be expected by chance (odds ratio 2.66 with a 95%-confidence interval between 1.7 and 6.0; $P = 0.01$). The associated between subthreshold brief depression and MDE is less strong (odds ratio 1.2 with a 95%-confidence interval between 0.6 and 2.4; $P = 0.05$) than between RBD and MDE. Current dysthymia was not diagnosed in any of the patients with either current MDE or current RBD or current subthreshold RBD. Therefore, and because of low prevalence rates of dysthymia, cases with dysthymia were discarded from all subsequent analyses.

This study compares subgroups of patients with particular depressive syndromes during the last 12 months to

Table 1 Patients in general practice by presence and absence of RBD, subthreshold RBD and MDE: sociodemographic characteristics, features of illness and treatment

	Depressive subtype					
	RBD + MDE	Sub-threshold RBD + MDE	RBD w/o MDE	Sub-threshold RBD w/o MDE	MDE w/o RBD or sub-threshold RBD	No MDE, no RBD, no dysthymia and no subthreshold RBD
Prevalences						
Number of identified patients	10	14	19	53	31	169
Reweighted prevalence rates	2.1%	4.1%	5.4%	18.0%	7.6%	62.8%
Sociodemographic characteristics						
Sex ratio (m : f)	2 : 8	5 : 9	1 : 18	16 : 37	9 : 22	69 : 100
Married	30.0%	35.7%	47.4%	39.6%	54.8%	52.0%
Mean age (years)	30.3	38.5	35.2	32.9	36.9	36.9
Psychological impairment						
Any psychological problem as reason for attendance	30.0%	28.6%	15.8%	9.4%	19.4%	4.7%
Psychological problem as main reason of contact	30.0%	14.3%	10.5%	3.8%	12.9%	1.8%
Weeks since main problem began (mean)	53.4	112.6	95.4	72.6	102.9	113.5
Mean GHQ score (28 items; mean, SD)	10.0 (5.2)	10.7 (7.0)	6.1 (3.8)	8.0 (6.0)	13.7 (6.4)	4.9 (3.3)
Mean GHQ score (12 items; mean, SD)	6.4 (2.9)	6.6 (3.6)	5.7 (3.5)	5.0 (3.6)	7.6 (3.7)	4.3 (5.4)
Social disability						
Global social disability (SDS)	65.6%	91.2%	84.8%	57.3%	73.9%	48.4%
Severe global social disability (SDS)	39.2%	4.4%	24.3%	7.8%	29.4%	5.1%
Disability in daily routine (SDS)	65.1%	86.5%	69.8%	38.8%	64.9%	37.2%
Severe disability in daily routine (SDS)	23.9%	10.0%	5.9%	6.8%	16.2%	3.7%
Deterioration of social relations (BDQ)	23.9%	57.7%	55.3%	44.7%	52.9%	27.5%
Severe or moderate deterioration of social relations (BDQ)	15.3%	4.4%	18.4%	1.0%	13.2%	1.9%
Number of days during last month unable to perform daily routine / BDQ (mean, SD)	3.9 (5.2)	7.0 (7.8)	3.2 (6.2)	6.5 (9.1)	9.4 (9.7)	4.0 (6.6)
Treatment						
Any current drug treatment	90.0%	78.6%	73.3%	82.1%	77.4%	78.4%
Any current psychotropic treatment	17.2%	8.8%	10.2%	6.8%	32.5%	9.5%
Any current antidepressant treatment	8.6%	4.4%	3.3%	2.0%	16.2%	2.4%

169 patients not reporting any depressive syndrome (i.e. no MDE, no dysthymia, no subthreshold RBD) during the last 12 months. Previous syndromes of depression remitted at least 12 months before the index assessment were reported by 54 of the 169 patients in this comparison group (reweighted 24.6%) of these 54, 31 patients reported a history of major depression, 11 reported a history of dysthymia, and 29 reported a history of recurrent brief depression. In order to prevent false-positive conclusions on the validity of RBD, an overconservative approach was given preference. Therefore, patients with a history of affected disorders but without depressive syndromes during the preceding 12 months remained in the comparison group.

Depressive disorders (all five subtypes with a diagnosis of depression) occurred more frequently among females than males, and particularly so in patients with RBD without major depression compared to patients without depression (chi-square 9.5; $P = 0.001$). Age was similar across all six comparison groups, with patients with major depression revealing the maximum mean age.

Psychosocial complaints and treatment

All groups of patients with depression reported increasingly severe health-related complaints as measured by the GHQ compared to patients without depression, with patients with MDE reporting maximum scores ($t = 8.1$; $P = 0.00$ for MDE; $t = 1.0$; $P = 0.10$ for RBD).

Patients with major depression and patients with RBD reported psychological problems as a reason for atten-

Table 2 Current comorbid psychiatric disorders (reweighted, %) by depressive subtype of patients in general practice

Comorbid psychiatric disorder (DSM-III-R)	Number of identified cases (unweighted)	Depressive subtype					
		RBD + MDE	Subthreshold RBD + MDE	RBD w/o MDE	Subthreshold RBD w/o MDE	MDE w/o RBD or subthreshold RBD	No MDE, no RBD, no dysthymia and no subthreshold RBD
Panic disorder or agoraphobia	20	17.2%	4.4%	3.3%	2.0%	16.8%	1.7%
Generalized anxiety disorder	41	43.5%	25.8%	10.2%	6.1%	40.6%	3.3%
Alcohol abuse or dependence	33	23.9%	24.3%	3.3%	10.0%	16.2%	10.0%
Somatization disorder	13	50.2%	8.9%	3.3%	0.0%	2.4%	1.4%
Hypochondriasis	4	0.0%	0.0%	0.0%	1.0%	2.4%	1.8%
Suicide attempts (lifetime)	40	23.9%	8.9%	16.1%	7.6%	12.0%	6.6%

dance significantly more frequently than patients without depressive disorders (chi square 8.6; $P = 0.02$ respectively chi square 5.1; $P = 0.01$).

The relative frequency of patients with any psychosocial impairment is very similar between the groups diagnosed with RBD without MDE and RBD with MDE. The comparisons to the nondepressed patients reveal significant results (chi-square 6.9 and 10.5; $P = 0.00$). Severe global psychosocial impairment, as measured by the Social Disability Schedule, is significantly elevated among patients with MDE (chi square 22.8; $P = 0.00$) compared to patients with no depression, particularly in patients with RBD and MDE. Although less strongly, RBD without MDE also shows a significant excess of severe social impairment (chi-square 10.5; $P = 0.01$). The same configuration emerges for the more specific components of global psychosocial impairment: any disability in daily routine is significantly more common among patients with RBD without major depression and among patients with MDE without RBD than among patients without depressive syndromes (chi-square 7.9 with $P = 0.01$ for MDE, and 6.8 with $P = 0.01$ for RBD). Severe disability in daily routine is significantly more common among patients with MDE without RBD than among nondepressed patients (chi-square 8.1 with $P = 0.004$). Although there was a trend in this direction, no significant difference with regard to severe disability in daily routine between patients with RBD without MDE and the nondepressed comparison group was observed (chi square 0.2 with $P < 0.10$). A similar configuration is observed for deterioration of social relationships, as measured by the self-rating scale BDQ: any deterioration is reported more frequently by patients with MDE with RBD and by patients with RBD without MDE than by nondepressed controls (chi-square 7.1 for MDE and 7.6 for RBD with $P = 0.01$ each). Moderate or severe deterioration of social relations (self-rating by BDQ) was more common among patients with MDE but without RBD and also among patients with RBD without MDE compared to patients without depression (chi-square 11.0 and 9.8 with $P = 0.001$).

Compared to patients without any depression, patients with MDE reported a significantly higher number of disability days during the last month (Table 1; $t = 3.86$; $df = 198$; $P = 0.001$). The number of disability days was also moderately enhanced among patients with subthreshold RBD without MDE ($t = 2.18$; $df = 220$; $P = 0.02$), whereas patients with RBD without MDE were not significantly different from patients without depression in this respect.

Only a minority of patients with MDE (32%) received psychotropic medication, with 16% receiving antidepressant treatment (Table 1). Both figures differ significantly from the corresponding treatment rates in nondepressed patients (chi-square 12.0; $P < 0.001$; chi-square 11.5; $P < 0.001$). However, neither patients with RBD nor patients with subthreshold RBD were substantially more often treated with psychotropic or antidepressant drugs (all four chi-squares lower than 0.5 with $P > 0.10$).

Comorbidity with psychiatric and somatic syndromes

Table 2 reports relative frequencies of psychiatric syndromes among subgroups of patients defined by occurrence of depressive syndromes during the last 12 months. Table 3 displays two modes of analyzing these figures. The prevalences of diagnoses are compared between the group of patients without any depressive syndrome (last column) and the groups of patients with MDE, RBD, and subthreshold RBD. The first strategy refers to the combined subtypes (i.e. ignores comorbidity between subtypes of depression) and uses the odds ratio statistics; the second strategy refers to the pure subtypes and uses chi-square tests.

A strong association between MDE and anxiety disorders during the last 12 months (Tables 2 and 3) is emerging from the association and from the odds ratio approach. An association between RBD and any generalized anxiety disorder results from the odds ratio analysis ($P = 0.05$), but does not hold up in the chi-square analysis comparing RBD without MDE with nondepressed patients ($P > 0.05$). The reason for these different conclusions is that the excess of generalized anxiety disorder among RBD patients is due mainly to an excess among the patients with comorbid RBD and MDE. Both MDE and RBD reveal excess comorbidity with somatization disorder by odds ratio analysis. It is apparent from Table 2 that these

Table 3 Odds ratios between depressive subtypes and other psychiatric disorders in patients in general practice. Confidence intervals (95%) in parentheses

Comorbid psychiatric disorder (DSM-III-R)	Odds ratios between depressive subtypes (not exclusive) and somatic disorders			Comparison of prevalences of somatic disorders between exclusive subtypes chi-square, *df* = 1		
	MDE	RBD	RBD or subthreshold RBD	MDE only vs no affective disorder	RBD only vs no affective disorder	Subthreshold RBD only vs no affective disorder
Panic disorder or agoraphobia	5.13 (2.06–12.78)	1.91 (0.57–6.43)	0.93 (0.36–2.43)	14.3**(*)	0.3	0.9
Generalized anxiety disorder	7.73 (3.81–15.68)	2.79 (1.17–6.68)	2.02 (1.04–3.91)	45.4***	1.0	0.0
Alcohol abuse or dependence	2.17 (0.98–4.79)	1.04 (0.32–3.36)	0.93 (0.43–2.00)	1.0	0.4	0.0
Somatization disorder	7.76 (2.54–23.71)	9.68 (3.12–30.03)	3.45 (1.15–10.38)	0.8	0.4	0.0
Psychogenic pain syndrome	2.47 (1.37–4.48)	1.60 (0.74–3.45)	1.56 (0.94–2.59)	0.3	1.8	0.6
Hypochondriasis	1.89 (0.27–13.10)	1.00 (0.05–19.04)	0.90 (0.13–6.16)	0.4	0.3	0.0

* $0.01 < P < 0.5$; ** $0.001 < P < 0.01$; *** $0.001 < P < 0.01$

Table 4 Current comorbid somatic disorders (reweighted, %) by depressive subtype of patients in general practice

Comorbid somatic disorder	Number of identified cases (unweighted)	Depressive subtype					
		RBD + MDE	Subthreshold RBD + MDE	RBD w/o MDE	Subthreshold RBD w/o MDE	MDE w/o RBD or subthreshold RBD	No MDE, no RBD, no dysthymia and no subthreshold RBD
Any chronic somatic disease	198	60.0%	78.6%	57.9%	67.9%	80.6%	63.7%
Heart disease	22	0.0%	8.9%	0.0%	5.5%	13.9%	5.6%
Hypertension	41	32.5%	8.9%	0.0%	5.1%	9.0%	14.4%
Asthma bronchiale	10	0.0%	0.0%	0.0%	1.0%	4.81%	5.1%
Diabetes mellitus	14	0.0%	4.4%	5.9%	2.0%	2.4%	6.5%

associations are due mainly to the elevated prevalence of somatization disorder in the group of patients with MDE and RBD. Consequently, the association between somatization disorder and MDE and RBD, respectively, does not hold up if the pure depressive subtypes are compared to the nondepressive condition (Table 3).

MDE was weakly associated with the coexistence of chronic somatic syndromes as assessed by the treating physician and without specification of the basic somatic disease ($P = 0.04$). Table 4 also reports specific ICD-10 diagnoses of somatic disorders. Although there was a trend for an association between current heart disease and MDE by odds ratio analysis – but not by chi-square test – (Table 5), there was no convincing evidence for a consistent and specific association between MDE and chronic somatic syndromes. In contrast to MDE, current chronic somatic syndromes and RBD were not more strongly associated than would be expected by chance. Lack of association was also observed between RBD and all particular somatic syndromes in Tables 4 and 5, with the only exception being hypertension; a weak association with hypertension was found with the pure RBD subtype, but not so when all patients with RBD were considered.

Frequency of episodes and depressive symptoms

Table 6 reports the number of episodes with depressed mood or loss of interest. These figures ignore the length of the episodes. As expected, Table 6 reports the highest number of episodes in the group of patients with both MDE and RBD during the last 12 months. RBD without MDE was characterized by a similar degree of recurrence. Simultaneously, brief episodes were also observed among patients in the comparison group, i.e. patients not allocated to MDE or to RBD or to subthreshold RBD. The mean duration of episodes is 3.4 (standard variation 3.1) in patients with RBD (without MDE) and also 3.4 (standard deviation 2.6) in patients with subthreshold RBD (without MDE).

Table 6 also reports the presence of symptoms considered as diagnostic criteria for MDE by the diagnostic

Table 5 Associations between somatic disorders and depressive subtypes (reweighted) in patients of general practitioneers

Comorbid somatic disorder	Odds ratios between depressive subtypes (not exclusive) and somatic disorders			Comparison of prevalences of somatic disorders between exclusive subtypes chi-square. $df = 1$		
	MDE	RBD	RBD or subthreshold RBD	MDE only vs no affective disorder	RBD only vs no affective disorder	Subthreshold RBD only vs no affective disorder
Any chronic somatic disease	1.12 (0.56–2.25)	1.16 (0.47–2.88)	0.66 (0.38–1.14)	3.4*	0.3	0.3
Heart disease	2.28 (0.90–5.75)	0.19 (0.01–3.15)	0.49 (0.17–1.40)	2.0	1.2	0.0
Hypertension	1.12 (0.50–2.54)	0.79 (0.25–2.55)	0.66 (0.31–1.39)	0.5	3.2*	2.9
Asthma bronchiale	1.29 (0.31–5.47)	0.42 (0.02–7.33)	0.32 (0.06–1.82)	0.2	1.1	1.1
Diabetes mellitus	0.87 (0.22–3.47)	1.00 (0.18–5.64)	0.89 (0.29–2.77)	0.5	0.0	1.6

* $0.01 < P < 0.5$; ** $0.001 < P < 0.01$; *** $0.001 < P < 0.01$

Table 6 Presence (%, reweighted) of depression associated symptoms during last 12 months (with duration of at least one day) in general practice patients by depressive subtype

	Depressive subtype					
	RBD + MDE	Subthreshold RBD + MDE	RBD w/o MDE	Subthreshold RBD w/o MDE	MDE w/o RBD or subthreshold RBD	No MDE, no RBD, no dysthymia and no subthreshold RBD
Number of episodes (mean, SD) with depressed mood or loss of interest	16.9 (5.1)	9.6 (2.9)	15.0 (9.0)	8.4 (4.0)	3.9 (10.7)	1.5 (4.7)
Symptoms associated with depression						
1) Depressive/dysphoric mood	100%	100%	100%	99.0%	97.5%	66.8%
2) Loss of interest/anhedonia	82.8%	78.9%	66.4%	49.2%	57.5%	16.0%
3) Appetite disturbances/weight changes	91.4%	100%	90.0%	88.9%	64.1%	51.4%
4) Sleep disturbances	100%	100%	96.7%	96.2%	92.7%	69.9%
5) Agitation/retardation	93.8%	95.6%	78.3%	75.5%	78.9%	33.8%
6) Loss of energy	58.9%	39.1%	32.1%	42.9%	46.3%	17.7%
7) Feelings of guilt/worthlessness	100%	63.4%	44.5%	49.2%	60.4%	34.5%
8) Reduced concentration	91.4%	92.1%	100%	94.9%	88.5%	49.7%
9) Ideation of death or suicide	91.4%	95.6%	96.7%	74.0%	73.1%	68.2%

manual DSM-III-R. Duration of symptoms and association with depressed mood or loss of interest were not taken into account. Thus, a relatively high proportion of patients in all groups suffered from these symptoms. Nearly all symptoms were significantly ($P = 0.05$) more frequent in the groups of patients with MDE only, RBD only, and subthreshold RBD, as compared with patients without depression. This configuration was not true, however, for item 3 (appetite disturbances), item 7 (feeling of guilt), and item 9 (ideation of suicide and death); only the MDE patients reported significantly more feelings of guilt compared to patients without depression (chi-square 7.9; $P = 0.005$), not patients with RBD or subthreshold RBD. Only patients with RBD or subthreshold RBD reported significantly more frequently appetite disturbances (chi-square 10.0; $P = 0.001$ respectively 23.4; $P = 0.00$), not patients with MDE (chi-square 1.8; $P = 0.13$). Ideation of suicide and death was more common among patients with RBD (chi square 5.8; $P = 0.01$), but not among patients with MDE (chi-square 0.4; $P = 0.3$). Similarly, a lifetime history of suicide attempts (Table 2) was most common among patients with current RBD (in particular, with RBD and MDE) compared to 6.6% among patients without depression; patients with MDE only were located in between. In general, RBD patients are characterized by fewer feelings of guilt and by more suicide ideation and attempts, as well as by more appetite disturbances, as compared with patients with MDE.

Subthreshold RBD

Subthreshold RBD behaved similarly to the more stringently defined RBD in all criteria under study, with an overall reduced degree of impairment and dysfunction. There was one exception to this rule: psychosocial impairment as measured by mean disability days was more severe among patients with subthreshold RBD only than among patients with RBD only. However, this exception may be due to random fluctuation. It is noteworthy that patients with subthreshold RBD are more psychosocially impaired than are patients without depressive disorders. Subthreshold RBD as well as RBD are not associated with current psychiatric and somatic disorders more frequently than would be expected by chance (Tables 3 and 5).

Discussion

The clinical validity of RBD: social impairment and comorbidity

Frequency, duration of episodes

This study provided evidence for the clinical validity of recurrent brief depression, although the appropriateness of the very stringent definition proposed by Angst et al. (1990) remains doubtful. This study replicated previous reports of a mean duration of brief episodes being about 3 days (Angst et al. 1990, Montgomery et al. 1992) and a recurrence rate of between 15 and 18 episodes per year (Montgomery et al. 1992). This similarity across studies is surprising, given the differences between the three settings.

Social impairment

Patients with current recurrent brief depression were more impaired by psychosocial functioning than patients without depressive disorders (as measured by less adjustment to daily routine). In this respect, the RBD patients were intermediate between the patients fulfilling the diagnostic criteria for MDE and the comparison group without current depressive syndromes.

Significant psychosocial impairment in patients with RBD was also reported by Angst et al. (1990) in a general population sample. However, in contrast to this study, Angst et al. (1990) found a similar degree of impairment in RBD and MDE. Sample differences may account for this quantitative discrepancy: self-selection is a characteristic feature of general practitioner studies. On the one hand, patients with significant psychosocial impairment may preferentially consult the general practitioner if they suffer from longstanding depression as MDE, but not when suffering from brief episodes, which might not be experienced by the patient as a disease even if it occurs as a recurrent condition. On the other hand, patients who are severely impaired by a psychiatric condition which is not tapped by standard diagnostic approaches may be preferentially transferred to psychiatrists. The lower percentage of patients with RBD reporting a psychological problem as a reason of contact compared to patients with MDE is compatible with this explanation. An alternative explanation is suggested by a lower degree of comorbidity between RBD and nonaffective disorders in the present study, compared to the study by Angst et al. (1990).

Comorbidity

As was observed in general population surveys (Angst et al. 1993), RBD during the last 12 months is strongly associated with major depression during the preceding year (odds ratio) and is not associated with concurrent dysthymia in primary care settings. The coexistence of diagnoses of RBD and MDE underscores the need to rule out concurrence of MDE as a reason for differences between RBD and nondepressed subjects. However, the psychosocial impairment reported by patients with RBD cannot be due exclusively to the concurrence of MDE. Patients with current RBD and no major depressive episode during the preceding 12 months were also significantly more subject to social impairment.

Excess comorbidity between RBD and other psychiatric or somatic disorders might also explain increased social disabiity. However, this study found a lack of significantly elevated comorbidity between RBD and psychiatric as well as somatic syndromes, whereas a strong association between MDE and anxiety disorders was found. This observation clearly argues that RBD does not just reflect the presence of other psychiatric or somatic disorders; in particular, the psychosocial impairment associated with RBD cannot be due to the concurrence of other well-established disorders with substantial psychosocial impairment.

Absence of comorbidity as detected in this study is surprising given the report from a general population sample by Angst et al. (1990), in which excess of panic disorder and substance abuse among subjects with the pure RBD subtype was found. Again, the two samples are not comparable, but comorbidity should predominate in treatment settings compared to the general population. One explanation for this discrepancy might be underreporting of nonaffective and somatic syndromes. However, this explanation is unlikely to be true, as major depression showed the expected excess comorbidity with anxiety disorders and with chronic somatic disorders (Ormel et al. 1991; van Hemert et al. 1993).

Thus, this study contributes to the evidence that RBD is a clinical entity associated with significant psychosocial impairment. This diagnostic entity cannot be substituted for by any of the established DSM-III-R diagnoses.

Clinical validity of RBD: relationship to suicidal tendencies

Subjects with the diagnosis of RBD carry an elevated risk for suicidal ideation and suicide attempts. The risk of suicide is most pronounced among subjects with MDE and RBD, with patients with RBD without MDE being at a higher risk than subjects with MDE but without RBD. This peculiar relationship between subtypes of depression and suicidality is not only observed in the present general practice sample, but also in the general population sample studied by Angst et al. (1990), and in the psychiatric outpatient sample studied by Montgomery et al. (1992). There is no report in the literature which is at variance with these observations. Thus, this configuration seems to be a rather universal one. Therefore, the new diagnostic category of RBD may serve as a major tool for the identification of subjects at elevated risk for suicide attempts. Longterm treatments to be developed for RBD should consider in particular the effects on suicide ideation and attempts.

Subthreshold RBD

Subthreshold RBD is characterized by reduced recurrency or by a more irregular recurrent course. This general practice study as well as the psychiatric outpatient study by Montgomery et al. (1992) observed a high proportion of erratical and irregular distribution of the multiple episodes over the last 12 months. In this study, the prevalence of brief depression with highly recurrent episodes during the last 12 months failing to meet the criterion of monthly occurrence was substantially greater (subthreshold RBD) than that of the stringently defined RBD. As is predictable from this constellation, the degree of symptomatic and psychosocial impairment was somewhat in between RBD and patients without current depression; the degree of impairment was still substantial compared to the group of nondepressed patients. These results argue for a less stringent definition of RBD than that proposed by Angst et al. (1990). For the requirement of monthly occurrence of brief depressive episodes, for example, could be substituted the requirement of nearly monthly occurrence (i.e. at least one episode in at least 10 months over a 12-month period). However, all operational definitions are to some extent artificial. Although there are currently no alternative operational definitions of diagnostic categories, the data presented are more compatible with the view that the degree of impairment varies continuously with the number of brief episodes during a defined time interval.

Treatment of RBD

Although patients with RBD are more psychosocially impaired than patients without depressive disorders, antidepressent drugs were not prescribed substantially more often to patients with RBD (in absence of major depression) compared to patients without any depressive disorder. Prescription of antidepressants was unexpectedly rare in general practice patients, given in the relatively high rate of current depressive disorders. Among the various comparison groups in this study, only patients with major depression received antidepression treatment signifcantly more often than patients without any depressive syndrome. The very low rate of antidepressant pharmacological treatment in patients with RBD but without MDE cannot be explained by the application of other psychological treatments. None of the 300 patients recruited for this study was involved in a specified psychotherapy treatment; other nonantidepressant psychotropic drugs were also not prescribed more often than to patients without any depressive syndrome.

The reasons for the undertreatment of RBD are unclear, given the data available from this study. One reason might be that general practitioners believe an efficient treatment to be lacking (Montgomery et al. 1992b). However, although efficacious treatments for this new condition have not yet been established, the efficacy of classical tricyclics prescribed on a long-term basis to control RBD still needs to be explored. In addition, reporting of psychological problems by the patient may be the main criterion for the general practitioner's choice of treatments. This cannot be the only explanation, however, since RBD patients mentioned psychological problems only slightly less often than MDE patients, and antidepressants are substantially more often prescribed in patients with MDE compared to those with RBD.

Both reasons might contribute to the lack – both absolute and relative to MDE – of specific antidepressant treatment. The observed undertreatment of RBD warrants the development of treatment strategies tailored to brief depression with a highly recurrent course. The substantial social impairment and increased risk of suicide ideation and acts in RBD patients underscore the need for appropriate treatment.

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Lack of efficacy of fluoxetine in recurrent brief depression and suicidal attempts

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Abstract Recurrent brief depression (RBD) fulfills DSM-III-R symptom criteria for major depression but the episodes are of shorter duration than the 2 weeks required by DSM-III-R. The clinical importance of the disorder has been observed in prophylactic studies of suicidal bahavior. The possibility that antidepressants with selective action on the reuptake of serotonin might be effective in preventing recurrences of brief depression has been investigated. Fluoxetine in a dose of 120 mg a week, administered biweekly, had no effect on the recurrence rate, which was maintained at approximately the same rate on fluoxetine (1 every 18.7 days) as with placebo (1 every 17.6 days). In a group of patients with two or more prior episodes of suicidal behavior, there were 18 attempted suicides in the 54 patients treated with fluoxetine and the same number in the 53 patients treated with placebo. Fluoxetine neither raised nor lowered the suicide attempt rate as compared with placebo, providing no evidence to support the drug's role in either suicide provocation or prevention. Since fluoxetine is clearly effective with recurrent major depression, it would appear that recurrent brief depression has a different pharmacology.

Key words Recurrent brief depression · Fluoxetine · Placebo · Suicide attempt · Prophylaxis

Introduction

Diagnostic classifications of depression currently in wide use define a syndrome of depression by requiring the presence of a minimum number of a specific list of symptoms, a defined duration of illness, and the exclusion of conflicting diagnoses. There has been general agreement among different classificatory systems concerning the defining symptoms of recurrent brief depression and the defining duration of illness has varied from 2 weeks according to DSM-III, DSM-III-R, Research Diagnostic Criteria of Spitzer et al. and ICD-10, to the longer 4-week period required in the criteria published by Feighner et al. (American Psychiatric Association 1987; American Psychiatric Association 1980; World Health Organization 1992; Spitzer et al. 1978; Feighner et al. 1972). These diagnostic criteria identify a group of patients suffering from major depression who have functional impairment and who are likely to respond to conventional antidepressant treatment. However, the criteria for major depression do not address the large number of cases that fulfill the syndromal definition of major depression but do not meet the requirement of at least 2 weeks' duration.

Until recently, there had been little systematic investigation of depressive states with a duration of less than 2 weeks, although their existence had been noted in the psychiatric literature (Paskind 1929; Gregory 1915). The early reports suggest that such episodes have a relatively high incidence; for example, 14% of one large sample of inpatients were reported to suffer from brief episodes of depression lasting from a few hours to a few days (Paskind, 1929). The Research Diagnostic Criteria of Spitzer et al. (1978) include a category that recognizes the existence of depressions that are intermittent but classifies them as minor depression in contrast to major depression, thus implying that it is a mild disorder of lesser importance.

More recently, brief episodes of depression have been recognized as being important in clinical populations because of their severity and associated impairment in functioning (Montgomery et al. 1989) and in epidemiological studies because of the high incidence. In the ongoing longitudinal studies of an enriched normal population sample by Angst and his colleagues, frequently recurring depressive episodes lasting less than 2 weeks were observed to

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have a prevalence at least as high as major depression (Angst and Dobler-Mikola 1985; Angst et al. 1990; Angst 1990). Similar rates of recurrent brief depression, i.e. brief episodes of depression lasting less than 2 weeks and occurring with a frequency of at least 12 episodes a year, have now also been reported in psychiatric and general practice populations (Maier et al. 1994; Lepine et al. 1994).

Clinical studies of recurrent brief depression

A mild but frequently occurring condition might not attract the attention of psychiatrists or focus investigation on the need for treatment. However, the clinical studies of recurrent brief depression show that it is not a mild disorder: most episodes are of moderate or severe intensity (Montgomery et al. 1989; Montgomery et al. 1990). The clinical importance of brief depressive episodes was noted in a series of studies designed to test the efficacy of treatment in reducing suicide attempts in a group of patients with a history of suicidal behavior (Montgomery et al. 1979; Montgomery et al 1983).

Patients with major depression were excluded from these studies, which used a prophylactic design, randomly assigning patients with a history of three or more suicide attempts to treatment for 6 months with placebo or a low-dose neuroleptic, flupenthixol given in a monthly i.m. dose of 20 mg, or, in a parallel study, with placebo or the antidepressant mianserin in a daily dose of 30 mg. The definition of preventing a suicide attempt was successful completion of the study period; a further suicide attempt was a treatment failure.

In spite of the exclusion of major depression at the start of the study, it was observed that during the study patients suffered short depressive episodes that lasted under 2 weeks. Patients were assessed at the start of the study and monthly using the Montgomery & Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979). The MADRS scores at the start of the study, which were low, as is consistent with periods of waiting for any present brief episode to resolve itself to ensure the exclusion of major depression, did not predict subsequent suicide attempts. However, at 4 weeks, the MADRS score representing the severity of the brief depression over the period, as well as individual items of the scale, were significant predictors of subsequent suicide attempts. The brief episodes of depression that were measured in the study were clearly associated with the suicide attempts; those patients with more severe brief depressions were at a greater risk. Furthermore the suicide attempts seemed to occur only during these brief depressions lasting less than 2 weeks.

The results of these placebo-controlled studies showed a significant advantage for the low-dose neuroleptic ($P < 0.01$) over placebo in reducing suicidal behavior. There was a reduction in suicide attempts in the group treated with the antidepressant compared with placebo but the difference was not statistically significant. These studies were designed to test the effect of pharmacological intervention on suicidal behavior and were not specifically directed at treatments that might affect brief depressive episodes. The apparent link between episodes of suicidal behavior and brief depressive episodes and the finding of an effective treatment that reduced suicidal behavior suggested that pharmacological treatment might be a possible strategy for both conditions.

Studies on the duration, recurrence and severity of RBD

A second stage of investigating the clinical nature of brief recurrent depression was carried out on a similar group of patients with a history of suicidal behavior during long-term follow-up. This was aimed at determining the frequency of the episodes and whether the episodes differed in an important way from major depression, apart from their brevity. Some patients with a history of suicide attempts but without major depression were followed up at intervals of approximately 2 weeks. Their history of depressive episodes was recorded and any episodes of depression of brief or longer duration occurring during follow-up were recorded and rated for length and severity. The results of this follow-up, reported elsewhere (Montgomery et al. 1989), confirmed that the episodes of brief depression occurred frequently, with a mean of approximately 20 episodes per year.

The episodes of brief depression were erratic in both their occurrence and the duration of the intervals between episodes. The intervals between the brief depression, measured from the beginning of one episode to the beginning of the next, varied substantially in duration, with a mean of 18 days. They lasted mostly between 1 and 5 weeks, with only 14% longer than 5 weeks.

The median duration of the individual episodes was 3 days. Two-thirds of episodes lasted between 2 and 4 days and 75% had a duration of 3 days or less. The mean severity of the episodes of depression measured by the MADRS score was 30.3, which is rather high, and 70% of the episodes could be categorized as moderate or severe. The episodes of recurrent brief depression appear to have the same symptoms as major depression and to be of similar or higher levels of severity. These findings contradicted the perception that brief depressions were largely mild.

Since the pattern of symptoms and the severity of the brief depression resembled major depression, it seemed possible that the use of an antidepressant might be an appropriate treatment approach. However, it seemed unlikely that currently available antidepressants with a delayed onset of action would be effective in the 2–4 days necessary to treat individual episodes. In the absence of rapidly acting antidepressants, efficacy needed to be tested in longer term prophylactic treatment where the treatments might reduce the rate of recurrence of episodes. The prophylacitc efficacy of a variety of antidepressants in major depression has been demonstrated in studies that have concentrated on measuring the recur-

rence rate in a group treated with an antidepressant compared to placebo (Montgomery and Montgomery 1992). This prophylactic design, similar to that used in the earlier study which showed the efficacy of flupenthixol in reducing suicidal behavior was adopted for the investigation of recurrent brief depression. Although it was apparent in the study that a high proportion of patients had brief episodes of depression, it had not been designed to specifically measure the duration. A preliminary analysis of a prophylactic study of fluoxetine is presented here.

Methods

Patients attending a psychiatric clinic with a history of 2 or more suicide attempts but who were not suffering from major depression according to the criteria of DSM-III-R were randomly allocated to double blind treatment for 6 months, given 60 mg fluoxetine or placebo twice weekly, and followed up at intervals of approximately 2–4 weeks. The length of any episode of depression occurring during follow-up was recorded. The severity of the episodes was rated using the MADRS. An episode of recurrent brief depression was defined as an episode of depression satisfying DSM-III-R criteria for major depression but which lasted less than 2 weeks. Suicide attempts occurring during the study were recorded. The preliminary results of the recurrence rate of the brief depressions and the suicide attempt rate are reported here.

Results

A total of 107 patients entered the study, 54 in the fluoxetine group and 53 in the placebo group. The proportion of patients who developed periods of brief depression during the 6-month study was high and the numbers of episodes of brief depression seen in each group were very similar. There were 153 episodes of brief depression lasting less than 2 weeks in the fluoxetine treated group compared with 157 in the placebo-treated group.

The length of exposure to treatment has to be taken into account in assessing differences between treatments (Table I). The recurrence rate, calculated as the number of episodes in relation to the length of exposure, was high in both groups. Expressed in terms of a 12-month period, there were 18 episodes per year in the fluoxetine-treated group compared with 17.6 in the placebo-treated group. There was no apparent significant difference between the groups.

The suicide attempt rate on placebo was high, with 18 attempts over the 6-month period. The suicide attempt rate in the fluoxetine-treated group was identical, with 18 attempts during the 6-month study period. The cumulative suicide attempt rate was 33.3% in the fluoxetine-treated group and 34% in the placebo treated group, with no apparent or significant difference between the groups (Table 2)..

Table 1 Recurrence rate of brief episodes of depression in patients treated with fluoxetine 20 mg twice weekly or placebo. No significant difference

	Fluoxetine $n = 54$	Placebo $n = 53$
Number of episodes	159	157
One episode per	18.7 days	17.6 days

Table 2 Suicide attempts occurring during 6-month study in fluoxetine- or placebo-treated patients

	Fluoxetine $n = 54$	Placebo $n = 53$
Suicide attempts	18	18
Suicide attempt rate	33.3%	34.0%

Discussion

The rate of recurrence of brief depressive episodes in this study was very similar to the recurrence rate reported in our earlier studies. In the present study, there were 18 episodes per year compared with 20 reported in the earlier studies. The difference between 18 and 20 episodes is not large and may be accounted for by random variation in the population. The population studied here has a rather high recurrence rate when compared with the epidemiological samples. It is possible that those with a history of suicide attempts and recurrent brief depression have a higher recurrence rate than those who do not.

Fluoxetine has been found to be effective in treating major depression in a large number of placebo-controlled studies in acute treatment (Stark and Hardison 1985; Montgomery 1989). It has also been shown in two large studies to have prophylactic efficacy in reducing the risk of new episodes of depression (Montgomery et al. 1988; Rosenbaum et al. 1993). The failure of fluoxetine in this study in recurrent brief depression, despite the large number of episodes observed during the study, indicates that fluoxetine is not an effective agent in treating recurrences of brief depression.

Fluoxetine in this study apparently had no effect on the course of illness in those suffering from recurrent brief depression or on the recurrence rate of the brief depressions. The failure to detect any evidence of efficacy of fluoxetine in recurrent brief depression in a long-term study is in sharp contrast to the clearcut demonstration of efficacy of fluoxetine in recurrent major depression (Montgomery et al. 1988; Rosenbaum et al. 1993).

The failure of fluoxetine to affect the suicide attempt rate, either by reducing or even raising it, is an important finding. The consistent observation of an association between low levels of 5-hydroxyindoleacetic acid in the cerebrospinal fluid and suicide attempts pointing to a serotonergic involvement in suicidal behavior has led investigators to speculate that treatment with selective serotonin reuptake inhibitors might reduce suicidal thoughts or behav-

ior. There is some evidence in major depression that such a strategy is effective in reducing suicidal thoughts (Wakelin 1988; Montgomery et al. 1981) and possibly suicidal acts (Beasley et al. 1991; Montgomery 1992). The absence of any beneficial effect of fluoxetine on the suicide attempt rate in this study, which had high morbidity, suggests that this group of patients with a combination of recurrent brief depression and recurrent suicidal behavior differs from major depression in an important way.

It is clear that in this study, fluoxetine neither increased nor decreased the suicide attempt rate. The absence of provocation of suicidal behavior by fluoxetine in this group of high-risk patients contradicts the suggestions that have been made on the basis of anecdotal reports that fluoxetine provokes suicidal behavior (Teicher et al. 1990). A high suicide-attempt rate, in line with previous placebo-controlled studies, was seen during placebo treatment in this group of previous suicide attempters and there was no difference between the active antidepressant and placebo. The high suicide-attempt rate observed on placebo emphasises the danger of bias in interpreting open report of suicidal behavior in those with a history of suicide attempts and makes it clear that judgments that particular treatments are likely to cause suicide attempts should only properly be made on the basis of randomized, placebo-controlled studies.

Concern about providing large numbers of capsules to a suicidally prone population prompted the adoption of a twice-weekly dosing regime. Fluoxetine, which has a half-life of 2–3 days, has an active metabolite with a very long half-life of around 7–10 days. This pharmacokinetic property of the drug was used to justify a safer intermittent dosage regime. An earlier study has shown that fluoxetine given in a dose of 60 mg once a week appears to be as effective as both fluoxetine given in a 60 mg daily dose and amitriptyline 150 mg. In that study, the plasma concentrations of norfluoxetine achieved during once weekly treatment were within therapeutic range. The decision to adopt a twice-weekly dosage regime of fluoxetine was taken in order to bring the dosage to within 120 mg per week, which would be in line with the recommended dose of 20 mg per day. The advantage of this regime was that the medication could be given under supervision in the clinic, thus providing less opportunity to overdose on the trial medication with obvious ethical advantages. A further advantage was the improved compliance with treatment.

The failure of fluoxetine in this study to affect either suicidal behavior or the recurrence rate of recurrent brief depression applies to this population and the dose studied. Nevertheless the failure to find any alteration in recurrence rate with a dosage regime which, from the results of earlier trials in major depression, is likely to be effective makes it unlikely that fluoxetine in the standard dose of 20 mg per day will prove effective in other samples.

It is of course possible that the failure to find efficacy might be due to chance factors. This is unlikely in this study, however, because of the very large number of episodes of brief depression seen in both the fluoxetine and placebo groups, and the absence of any detectable treatment effect. Another explanation might be the unusual dose used or that a dose equivalent to 20 mg a day was too low. However, in view of the demonstration of efficacy of fluoxetine in a wide range of doses from 5 mg to 80 mg a day in placebo-controlled studies in the acute treatment of major depression this seems unlikely.

The conclusion from this study is hard to escape. Fluoxetine, which is an effective treatment in major depression, does not seem to be effective in recurrent brief depression. The results are in accord with a study in a population with better defined recurrent brief depression. A preliminary analysis of a similar study of paroxetine in a dose of 20 mg a day is reported to show no evidence of efficacy compared with placebo in a 6-month prophylactic study (Montgomery et al. 1993).

The result have important clinical implications. They suggest that SSRIs are probably not effective, a conclusion that raises uncomfortable questions as to the efficacy of other antidepressants. The results of these studies are supported by the reported failure of these patients to find any effective treatment for their disorder and the generally negative reports of efficacy with traditional antidepressants. Without positive evidence of efficacy of an antidepressant in recurrent brief depression, it is inappropriate to recommend their use in the treatment of the condition.

The results remind one of the basis of the recommendation that major depression be defined by the persistence of the symptoms for 2–4 weeks. This criterion was developed to help define the population of depressions that were found to respond to conventional antidepressants and to exclude those who were thought not to respond. To some extent, these present findings suggest that this proposition was correct and recurrent brief depression has a different pharmacology and therefore probably a different biological basis.

For the clinician, it is now clearly important to distinguish between those with recurrent brief depression and those with major depression, since there are no grounds to expect an antidepressant response in the former group. In deciding whether antidepressant treatment is appropriate, careful attention should be paid to the duration criterion so that those with brief episodes are not given inappropriate treatment. A question that remains to be addressed is the problem of how to treat those with combined depression, that is, brief depression coexisting with major depression. We cannot assume response and it is possible that presence of brief depression identifies a population that is not responsive to antidepressants.

One is reminded by the results of this study of the poor response in another category of depressed patients, namely those with rapid-cycling bipolar illness. Antidepressants are reported to be ineffective in this group and in some cases to provoke ultra-rapid cycling. One perception of recurrent brief depressions could be the unipolar version of bipolar ultra-rapid cyclers. In that population, there are suggestions that mood stabilizers such as lithium and sodium valproate may be effective and these drugs may therefore be considered as candidate

treatments that meed to be investigated in recurrent brief depression.

There is currently little evidence of efficacy for any antidepressant in recurrent brief depression, which leaves the clinician with the dilemma of what advice to provide. In view of the associated substantial risk of suicide attempts, it would seem wise to avoid any toxic treatments since the likelihood of benefit is low. Recurrent brief depression is now recognized in the international classification of disease ICD-10, and sufferers, who report that they may have been considered malingerers or as personality disorders, experience relief from the realization that this a common disorder and not a figment of their imagination. Even so, with the present state of knowledge, there is no treatment. At the moment it seems that the best we can do is to provide common-sense advice on life style, including advice to avoid difficult decisions or confrontations during the episodes of depression.

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Expert Opinion

Central & Peripheral Nervous Systems

Higher than Physician's Desk Reference (US) doses on atypical antipsychotics

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The Physician's Desk Reference (PDR) was established to provide for the practicing of a complete listing of all medications with the FDA-approved labelling, including dosage recommendations. Perhaps in order to maximise individual usage of medications, pharmaceutical companies have frequently targeted lowest possible doses for FDA approval. However, many patients with a variety of illnesses due to resistance and/or multiple illnesses, may need higher than these dose ranges to maximise therapeutic response. In terms of regularly prescribed atypical antipsychotics released over the past 10 years, only risperidone initially obtained approval for a dose for psychosis (16 mg) higher than that suggested currently (maximum of 8 mg). The dose that was approved for mania was lower: a maximum of 6 mg. The others: respectfully, olanzapine (schizophrenia:15 mg, mania:20 mg), quetiapine (schizophrenia: 750 mg; mania: 800 mg), ziprasidone (schizophrenia and mania: 160 mg) and aripiprazole (schizophrenia and mania: 30 mg) obtained approvals for psychosis that may limit adverse events but, at the same time, limit benefits. Other data from various sources (double-blind trials, open-label trials, reviews and case reports) have found safety and/or efficacy for the following maximum doses: olanzapine (40 mg), quetiapine (1600 mg), ziprasidone (320 mg) and aripiprazole (75 mg). Reports above those doses are included, but either are insufficient in numbers or bring up questions on safety. In many situations, feared increase in adverse events were not magnified by use of higher doses.

Keywords: antipsychotic, aripiprazole, bipolar disorder, dosing, olanzapine, quetiapine, risperidone, treatment, ziprasidone

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1. Introduction

The Physician's Desk Reference (PDR) [1] is now in its 57th edition in the US. It was originally developed, and has continued to be, the standard for physicians in the US to have easy access to provide 'an exact copy of the product's FDA-approved labelling.' The listing, under the Code of Federal Regulations 201.100(d)(1), requires that dosages listed for each medication be in the 'same language and emphasis' as found in the approved FDA labelling. At the same time, the FDA recognises that the federal Food, Drug and Cosmetic Act does not limit the manner in which a physician may use an approved drug. The PDR annually updates the full text as well as issuing updates throughout the year to practicing physicians, as the FDA approves new medications while, at the same time, adding warnings to others. For example, in the past year, warnings were added to the use of antidepressants in paediatric populations.

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Pharmaceutical companies have often, perhaps in the interest of limiting theoretical and real risk of adverse events, presented to the FDA data showing efficacy at lowest possible dosages. These results are based on studies of pure populations, generally a minority of those seen in real practice. The latter, for example, include treatment-resistant patients, those with multiple diagnoses. They might be expected to require higher-than-usual doses of the agent received.

Among antipsychotics, the earliest one developed and released was chlorpromazine (in the 1950s). However, the current PDR write-up is based on a revision in 2002 because the owner of the brand name produced a new form for commercial release. In recent years, the release of atypical antipsychotics in common use in the US have included: risperidone, olanzapine, quetiapine, ziprasidone aripiprazole. Clozapine has been excluded from this review as its use has declined over time, and it is well known for having dosing limited by blood level as well by monitoring of white blood count with a risk of seizures.

2. Current limits in the Physician's Desk Reference and related safety information

PDR dosing limits are adjusted by several factors – diagnosis, age and medical condition of the patient. For details on adverse events, see Table 1.

2.1 Risperidone

Risperidone efficacy in schizophrenia was established in six to eight week controlled trials. The maximum doses suggested for treatment by the FDA are 16 mg/day for schizophrenia and mania. In schizophrenia, it is further said that doses up to 16 mg/day have been used, but they were not found more efficacious than 8 mg/day. It reports on 4 trials that utilised doses with maximums of 8 mg/day (1 study) [2], 10 mg/day (1 study) [3], and 16 mg/day (2 studies) [4,5]. For 'long-term efficacy', it reports on a trail with a maximum dose of 8 mg/day [6]. In acute mania monotherapy, 2 trials are presented with a maximum dose of 6 mg/day [7,8]. In mania as add-on therapy to lithium or anticonvulsants, two studies are presented with a maximum dose of 6 mg/day [9,10]. Adverse events that were most evident in general at ≤ 10 mg/day in acute trials [2-5] (16 mg/day will be reviewed under higher doses) in schizophrenia were insomnia, agitation and extrapyramidal symptoms (EPS) , as reported in the PDR. In bipolar mania [7-8] (where the maximum dose was < 10 mg/day), side effects reported more frequently for risperidone than placebo were somnolence, dystonia and akathisia. In adjunctive therapy studies in bipolar mania [9-10], most frequent reports were found for somnolence, dizziness and parkinsonism (see Table 1a).

2.2 Olanzapine

Olanzapine efficacy in schizophrenia was established in 2 short-term (6 week) controlled trials of in-patients [11,12]. In the first, a 10 mg daily dose was found to be superior to placebo on the positive and negative symptom scale (PANSS) total score; in the second, the two highest doses – 12 and 16 mg/day were found to be effective. The maximum dose suggested by the FDA is 15 mg/day; however, it is stated that doses > 10 mg/day were not found to be more efficacious. In monotherapy in bipolar disorder [13,14], results are presented on one 3 week study and one 4 week study. Each study allowed a range of 5 – 20 mg/day. It only states that doses > 20 mg/day have not been evaluated for safety. Results on two combination trials of olanzapine versus placebo add-on to either lithium or valproate for inadequately controlled manic or mixed symptoms are also presented [15,16]. Doses used were in the 5 – 20 mg/day range. FDA concluded that 10 mg/day should be the initial dose with maximum at 20 mg/day. There were also three studies, two in schizophrenia [17,18] and one in bipolar disorder [19] of the use of intramuscular olanzapine. Doses used were either a range (2.5, 5, 7.5, 10 mg) in a single administration versus placebo [17] or a single dose of 10 mg [18,19] versus placebo. The most frequent adverse events reported for olanzapine in schizophrenia studies [11,12] were postural hypotension, constipation, and weight gain. In the bipolar mania monotherapy studies [13,14], the results were asthenia, dry mouth and constipation. Investigation into dose-dependence in adverse reactions in acute trials in schizophrenia showed increases in extrapyramidal events from 5 to 15 mg/day. The dose ranging study in intramuscular preparation [17] showed no dose-dependent adverse reactions (see Table 1b).

2.3 Quetiapine

Quetiapine approval for schizophrenia is based on three six-week protocols determined in large part on the brief psychiatric rating scale (BPRS) changes [20-22]. The FDA position on dosage and efficacy is mixed but states 'in other studies, however, doses in the range of 400 – 500 mg/day appear to be needed'. Then, it states based on the protocols, that the 'safety of doses above 800 mg/day have not been evaluated in clinical trials.' The three studies were: 1) contrasting 5 doses of quetiapine (75, 150, 300, 500, 750) with the results that the 3 top doses all showed efficacy [20]; 2) contrast of high (up to 750 mg/day) and low (up to 250 mg/day) doses with only the high-dose group (mean of 500 mg/day) showing efficacy [21]; and 3) contrast of 450 mg/day versus 50 mg/day with only the higher doses displaying efficacy [22]. The two studies done in bipolar disorder for monotherapy for 12 weeks used a range of 400 – 800 mg/day [23,24]. This is the same range concluded for dosing by the FDA. The protocol for adjunctive treatment in bipolar mania [25] lasted only 3 weeks also had a range of 400 – 800 mg/day, with a similar FDA conclusion. The most frequent adverse events reported in the FDA summary found in all monotherapy trials [20-24] were headache, somnolence and dizziness (see Table 1c).

2.4 Ziprasidone

With regard to ziprasidone, 5 studies [26-30] were conducted in schizophrenia upon which the FDA concluded that there

Table 1a. Adverse events by risperidone within PDR dose limits (% versus placebo).

	Schizophrenia (< 10 mg/day) [2-5]	Mania (< 10 mg/day) [7,8]	Adjunctive mania [9,10]
Insomnia	29 vs. 23		
Agitation	22 vs. 20		
EPS	17 vs. 16		
Headache	14 vs. 12		
Somnolence	3 vs. 1	28 vs. 7	25 vs. 12
Akathisia		16 vs.6	8 vs. 0
Dizziness		11 vs. 9	14 vs. 2
Dyspepsia		11 vs. 6	
Nausea		11 vs. 2	
Parkinsonism		6 vs. 3	14 vs. 4
Abnormal vision		6 vs. 2	
Increased saliva			10 vs. 0
Diarrhoea			8 vs. 4
Dystonia			6 vs. 4
Abdominal pain			6 vs. 0

EPS: Extrapyramidal symptom; PDR: Physician's Desk Reference.

Table 1b. Adverse events by olanzapine within PDR dose limits (% versus placebo)

	Schizophrenia [11,12]	Mania [13,14]	Combination mania [15,16]
Postural hypotension	5 vs. 2		
Constipation	9 vs. 3	11 vs. 5	8 vs. 4
Weight gain	6 vs. 1		26 vs. 7
Dizziness	11 vs. 4	18 vs. 6	14 vs. 7
Akathisia	5 vs. 1		
Asthenia		5 vs. 1	
Dry mouth		22 vs. 7	32 vs. 9
Dyspepsia		11 vs. 5	
Increased appetite		6 vs. 3	24 vs. 8
Somnolence		35 vs. 13	
Tremor		6 vs. 3	
Back pain			8 vs. 4
Speech disorder			7 vs. 1
Increased salivation			6 vs. 2
Amnesia			5 vs. 2
Parethesia			5 vs. 2

EPS: Extrapyramidal symptom; PDR: Physician's Resk Reference.

Table 1b. Adverse events by olanzapine within PDR dose limits (% versus placebo) (continued)

	Schizophrenia [11,12]	Mania [13,14]	Combination mania [15,16]
Schizophrenia: dose-dependent side effects (%)	*5 mg*	*10 mg*	*15 mg*
Any EPS	15	25	32
Asthenia	8	9	20
Dry mouth	3	5	13
Nausea	0	2	9
Somnolence	20	30	39
Tremor	0	5	7

EPS: Extrapyramidal symptom; PDR: Physician's Resk Reference.

Table 1c. Adverse events by quetiapine within PDR dose limits (% versus placebo).

	Monotherapy (schizophrenia and mania)	Adjunctive
Headache	21 vs. 14	
Somnolence	18 vs. 8	34 vs. 9
Dizziness	11 vs. 5	
Dry mouth	9 vs. 3	19 vs. 3
Constipation	8 vs. 3	10 vs. 5
Asthenia		10 vs. 4
Abdominal pain		7 vs. 3
Weight gain		6 vs. 3

PDR: Physician's Desk Reference.

Table 1d. Adverse events by ziprasidone within PDR dose limits (% versus placebo).

	Schizophrenia	Mania
Somnolence	14 vs. 7	31 vs. 12
EPS	14 vs. 8	31 vs. 12
Respiratory tract infection	8 vs. 3	
Dizziness		16 vs. 7
Akathisia		10 vs. 5
Abnormal vision		6 vs. 3
Asthenia		6 vs. 2

EPS: Extrapyramidal symptom; PDR: Physician's Desk Reference.

Table 1e. Adverse events by aripiprazole within PDR dose limits (% versus placebo).

	Schizophrenia	Mania	Schizophrenia and mania
Somnolence	15 mg; 8.7 20 mg; 7.5 30 mg; 15.3 PBO; 7.7		
EPS	17 vs. 12		
Constipation		13 vs. 6	
Akathisia		15 vs. 4	12 vs. 5
Headache			31 vs. 26
Nausea			16 vs. 12
Vomiting			11 vs. 6
Light-headedness			11 vs. 8

EPS: Extrapyramidal symptom; PBO: Placebo; PDR: Physician's Desk Reference.

were 'trends toward dose response within the range of 20 – 80 mg b.i.d' and again, stated that 'the safety of doses above 100 mg b.i.d has not been systematically evaluated in clinical trials'. Individually, the 5 studies showed: 1) a 4-week trial in which 60 mg b.i.d, but not 20 mg b.i.d, showed significance versus placebo; 2) 80 mg b.i.d had a numerically but not statistically greater effect than 40 mg b.i.d in a 6-week trial versus placebo; 3) no clear evidence for dose-response relationship from 20 mg b.i.d to 100 mg b.i.d in another 6-week trial (except in PANSS negative subscale, where only 100 mg b.i.d showed statistical superiority over placebo); 4) a 4-week trial in which none of 3 doses (10, 40 and 80 mg/day) showed benefit over placebo; 5) a maintenance study of 52 weeks in which 20, 40 and 80 mg b.i.d all showed benefit over placebo in preventing relapse. In bipolar mania, the FDA suggests efficacy in the range of 40 – 80 mg b.i.d. This is based on two 3-week trials [31,32], each with a titration range of 40 – 80 mg b.i.d; patients in the first study were placed on 80 mg b.i.d on the second day. The mean dose for the studies were 132 mg/day, and 112 mg/day, respectively. The most common adverse events for the short-term schizophrenia trials were: somnolence, extrapyramidal symptoms, and respiratory tract infection. In the acute bipolar mania studies, the most common reports were for somnolence, extrapyramidal symptoms and dizziness (see Table 1d).

2.5 Aripiprazole

Regarding aripiprazole, the FDA states that although it has been used in schizophrenia trials in a dose range of 10 – 30 mg/day, doses > 10 – 15 mg/day were not more effective than the minimal ones used. It also reports that there were four short-term trials [33-36], three of which separated from placebo. The studies were as follows: a) a 4-week study using 15 and 30 mg/day doses of which both showed significance; b) a 4-week trial with doses of 20 and 30 mg/day in which both showed efficacy; c) a 6-week protocol showing effectiveness at 10, 15 and 20 mg/day; and d) a 4-week trial with a dose range of 5 – 30 mg/day which did not separate from placebo. In bipolar mania, the FDA can only conclude that 30 mg/day is effective because that was the starting dose. This is followed by the standard statement 'safety of doses above 30 mg/day has not been evaluated'. This is based on two 3-week protocols [37,38] with a starting dose of 30 mg/day, although patients could be reduced to 15 mg/day. There was no evaluation done by final dosage. In schizophrenia, a dose-related adverse event is somnolence. In bipolar mania, most frequent were constipation and akathisia. In combining schizophrenia and bipolar mania, common reports were headache, nausea and akathisia (see Table 1e).

3. Use of atypical antipsychotics above usual range

This section in historical sequence reviews the available information on use of each of the current five atypical antipsychotics in terms of available information (double-blind, open-label and case reports) above usual ranges (see Table 2). It is well-recognised that as a consequence, conclusions can only be suggestive and in virtually all cases would require replication in double-blind studies. Real world patients, in contrast to those participating in clinical studies, may require higher than usual doses to respond, based on a number of factors, for example, severity of psychosis or mania, weight and rate of metabolism.

See detail on study reports for both efficacy and adverse events in Table 2.

3.1 Risperidone

As seen above, the FDA statement concerning risperidone is that although it has been used up to 16 mg/day in schizophrenia, doses > 8 mg/day were not found more efficacious. One of these papers showed that response at 16 mg/day was similar to response at 6 mg/day in terms of percentage of patients showing reductions of at least 20% in the PANSS score (51 versus

57%), fall in total PANSS score (14.5 versus 16.1) and fall in BPRS (8.7 versus 9.6) [4]. However, the same trial showed that 10 mg/day results were worse than findings at both 6 mg/day and 16 mg/day. The other trial [5] showed that maximum reductions in PANSS and BPRS took place at 6 mg/day (25.7, 16), followed by 16 mg/day (14.3, 8), and then 10 mg/day (10.6, 6). Regarding mania and dosage, there appear to be no reports at use at doses > 6 mg/day. The adverse events picture in psychosis is also somewhat baffling, as the net change in EPS for one trial [4] is similar for the 6 mg/day and 16 mg/day dose – an increase of 2.9, whereas that at 10 mg/day is significantly less at 2.0. The other trial [5] showed worsened Parkinsonism induced at 10 mg/day with the other three doses had rates similar to placebo.

3.2 Olanzapine

In contrast to risperidone, there are many case reports, case series, open-label and controlled studies for the use of olanzapine above usual dosage concentrations. There are a series of double-blind trials in schizophrenia that utilised doses > 15 mg/day [39-42]: 1) an 8-week study of treatment resistance that used a dose of 25 mg/day (versus chlorpromazine at 1200 mg/day); 2) an 18-week study of treatment resistance with a dose range of 15 – 25 mg/day (versus clozapine 200 – 600 mg/day); 3) a 14-week study with a history of 'suboptimal treatment response' at a dose of 20 mg/day – which at the end varied from 10 to 40 mg/day (versus clozapine 500 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day); and 4) a 16-week cross-over study in treatment resistance at 50 mg/day (versus clozapine 450 mg/day). In the first study, no statistically significant difference was found between the two treatments in primary outcome measures: BPRS, scale assessment negative symptoms (SANS), and clinical global inventory (CGI) ($p = 0.09$). Response criteria were met by 7% of those treated with olanzapine, but none treated with chlorpromazine. The second study showed no significant difference between the two groups in change in PANSS total score. Numerical superiority was shown for olanzapine in the PANSS, BPRS (1 – 7), and CGI-S (severity). Treatment response showed the same directions: olanzapine: 59.6%; clozapine: 54.0%. (based on the usual minimum of 20% reduction in the total PANSS score). In the third study, at the end of 14 weeks, olanzapine, clozapine and risperidone, but not haloperidol, showed significant reductions in the PANSS Total score; only clozapine displayed significant improvement in the PANSS negative symptom score. Perhaps, more importantly, although the improvements were modest, only olanzapine showed further improvement after dose was increased during weeks 9 – 14 (maximum risperidone was 16 mg/day, clozapine 800 mg/day and haloperidol 30 mg/day). In the final cross-over study, change in the mean BPRS was reduced by 20% in 30% of the clozapine and in none of the olanzapine patients.

In open-label trials, of which there have been 6 [43-48], time of administration lasted from 6 weeks to 1 year, with a range of maximum doses from 25 to 40 mg/day. Overall, in studies with predominant dosing at levels greater than approved levels, significant results were: 1) 50% rate of treatment response at a mean dose of 28 mg/day [43]; 2) significant improvement in total, positive and negative symptoms when 64% received modal dose of 25 mg/day [44]; 3) 40% treatment response rate in a treatment resistant sample with 67% receiving 25 mg/day [45]; 4) at range of 10 – 40 mg/day (mean dose 24.8 mg/day), moderate improvement in total PANSS [46]; 5) no change in total score, but significant improvement in PANSS cognitive factor (0.92, $p < 0.01$) [47]; and 6) in long-term study, statistically significant improvement in CGI-S score with reduced hospital admissions and length of stay [48]. Furthermore, most patients showed improvement in either or both of positive and negative symptom clusters. In those studies that broke down responses at doses greater or less than 20 mg/day, doses > 20 mg/day were found preferable in 1) overall response [43], 2) PANSS cognitive and depression/anxiety score [46]. In terms of worsening, two trials [47,48] showed worsening of PANSS excitement factor at higher doses (-1.36; $p < 0.053$). Finally, as expected, case reports [49-59] showed generally positive responses at doses up to 80 mg/day, and the one report that focused on treatment resistance to clozapine, risperidone and conventional antipsychotics in a retrospective chart review found moderate-to-marked improvement in 71% that had taken conventional antipsychotics and 40% that had been clozapine-resistant [49] at doses up to 60 mg/day.

In terms of tolerance and safety, the double-blind studies showed that olanzapine was generally well-tolerated in comparative studies. In the comparison trial versus chlorpromazine [39], the olanzapine group had fewer cardiovascular and motor adverse events, as well as, in contrast to the chlorpromazine group, no use of antiparkinsonian drugs. There have been three trials contrasting olanzapine with clozapine [40-41,60]. The first showed overall results which showed that treatment emergent events were greater in the clozapine group (increased salivation, constipation, nausea, dizziness, tooth disorder) than in the olanzapine group (dry mouth). Further, there was greater improvement in EPS in the olanzapine group. Weight gain was somewhat greater in the clozapine group (2.3 vs 1.8 kg); prolactin levels increased in olanzapine versus clozapine groups (+ 0.18 nmol/l versus -0.14 nmol/l, $p = 0.02$), but its clinical significance is questionable. The next study showed no differences among the various antipsychotics in rates of EPS; use of benztropine after 8 weeks, was greatest in the risperidone group (29.3%) versus clozapine (7.5%) and olanzapine (5.1%). Weight gain was greatest with olanzapine, followed by clozapine, risperidone, haloperidol. The third comparison study [42,60] showed that during the initial eight weeks, patients taking olanzapine had numerically more weight gain than those taking clozapine. Side effects that differentiated the two treatments included: dry mouth (olanzapine > clozapine, $p < 0.05$), sialorrhoea (clozapine > olanzapine, $p < 0.05$) and blurry vision (olanzapine > clozapine, $p < 0.09$). Metabolic parameters had numerical differences that did not reach statistical significance (see details, Table 2). With regard to the open studies, the increased doses most commonly related

Table 2a. Finding of reports at use greater than PDR doses (risperidone).

Type (n)	Diagnosis (age)	Dose (mg/ day)	Results								Ref
			PANSS	*BPRS*	*EPS total*	*Somnolence*	*Headache*	*Dizziness*	*Insomnia*	*Agitation*	
DB (388)	Schizophrenia (37.4)	PBO	3.3	1.9	2.4	0	4.5	0			4
		2 (risperidone)	-1.8	-1.6	2.3	3.2	7.9	3.2			
		6 (risperidone)	-16.1	-9.6	2.9	3.1	15.6	9.4			
		10 (risperidone)	-8.9	-5.6	2.0	3.1	12.3	1.5			
		16 (risperidone)	-14.5	-8.7	2.9	4.5	7.6	0			
		20 (haloperidol)	-4.1	-3.3							
DB (135)	Schizophrenia (37)	PBO	4.6	3.2	2.3		18.2		36.4	45.5	5
		2 (risperidone)	-11.1	-6.3	2.3		25.0		58.3	41.7	
		6 (risperidone)	-25.7	-16.0	2.1		22.7		54.5	54.5	
		10 (risperidone)	-10.6	-6.0	7.5		13.6		54.5	40.9	
		16 (risperidone)	-14.3	-8.0	2.3		12.5		58.3	58.3	
		20 (haloperidol)	-9.3	-5.4	8.6		23.8		66.7	57.1	

BPRS: Brief psychiatric rating scale; DB: Double-blind; EPS: Extrapyramidal symptom; PANNS: Positive and negative symptom scale; PBO: Placebo; PDR: Physician's Desk Reference.

Table 2b. Finding of reports at use greater than PDR doses (olanzapine, double-blind trials)

Type (n)	Diagnosis (age)	Results					Ref
			25 mg/day olanzapine	***1200 mg/day chlopromazine***			
DB (84)	Schizophrenia Treatment-resistant (42.8)	BPRS total	-1.4	1.4			39
		SANS	-41	-38.7			
		Simpson-Angus	0	-0.4			
		Barnes akathisia	-2.1	-1.3			
		Dry mouth (%)	38.1	73.8			
		Drowsiness (%)	35.7	52.4			
		Headache (%)	28.6	19.0			
		EPS (%)	28.6	50.0			
		Dizziness (%)	14.3	16.7			
		Insomnia (%)	14.3	4.8			
			15 – 25 mg/day olanzapine	***200 – 600 mg/day (clozapine)***			
DB (180)	Schizophrenia (38.6)	PANSS total	-25.6	-22.1			40
		BPRS (1 – 7)	-15.2	-14.0			
		Solicited adverse events (%, $p < 0.05$ between treatments)					
		Drowsiness	25.8	47.7			
		Hypersalivation	14.6	62.8			
		Dry mouth	27.0	12.8			
		Dizziness	6.7	30.2			
		Increased perspiration	9.0	22.1			
		Hypotonia	2.2	10.5			
		Tardive dyskinesia	5.6	0			
		Simpson-Angus	-3.2	-1.4			
		AIMS	-0.8	-0.7			
		Barnes akathisia	-0.3	-0.4			
			30.4 mg/day olanzapine	***526.6 mg/day clozapine***	***11.6 mg/day risperidone***	***25.7 mg/day haloperidol***	
DB (157)	Schizophrenia, schizoaffective (18 –60)	PANSS total	-3.4	0.9	0.4	0.2	41
		PANNS negative	-0.5	0.4	0	0.2	
		Weeks 9 – 14 EPS	0.1	-0.2	0.2	-0.3	
		Weight gain (kg)	5.4	4.2	2.3	0.2	

AIMS: Abnormal involuntary movement scale; BPRS: Brief psychiatric rating scale; CGI: Clinical global inventory; DB: Double-blind; dFBS: Change in fasting blood sugar; EPS: Extrapyramidal symptom; PANSS: Positive and negative symtom scale; PDR: Physician's Desk Reference; SANS: Scale assessment negative symptoms; SAS: Social adjustment scale.

Table 2b. Finding of reports at use greater than PDR doses (olanzapine, double-blind trials) (continued)

Type (n)	Diagnosis (age)	Results			Ref
			50 mg/day olanzapine	*450 mg/day clozapine*	
DB (13, cross-over)	Schizophrenia Treatment-resistant (40.3 [clozapine–olanzapine], 35.9 [olanzapine–clozapine])	BPRS total	-1.00	-6.50	42
		Change in CGI	0.13	-0.2	
		Discontinuation treatment	6/13	0/10	
		Weight (lb)	7.5	3.4	
		SAS	0.3	-1.3	
		Akathisia	15%	20%	
		Dry mouth	62%	20%	
		Dyspepsia	23%	70%	
		Lethargy	46%	90%	
		Sialorrhoea	46%	90%	
		Sweat	8%	50%	
		Side effects rate (without cross-titration) (%)			60
		Dry mouth	80	20	
		Sialorrhoea	10	80	
		Blurry vision	40	0	
		dFBS	+4	+12	
		Total cholesterol	+2	+18	
		Triglycerides	+5	+92	

AIMS: Abnormal involuntary movement scale; BPRS: Brief psychiatric rating scale; CGI: Clinical global inventory; DB: Double-blind; dFBS: Change in fasting blood sugar; EPS: Extrapyramidal symptom; PANSS: Positive and negative symtom scale; PDR: Physician's Desk Reference; SANS: Scale assessment negative symptoms; SAS: Social adjustment scale.

Table 2c. Finding of reports at use greater than PDR doses (olanzapine, open-label trials)

Type (n)	Diagnosis (age)	Dose (mg/day)	Results				Ref
			Week	*BPRS*	*GAS*	*AIMS*	
OL (16)	Schizophrenia Treatment-resistant (40)	5 – 40 (11/16 > 20 mg/day)	0	71	30	25	43
			4	65	35	35	
			8	60	40	30	
			16	50	43	25	

AIMS: Abnormal involuntary movement scale; BPRS: Brief psychiatric rating scale; CGI-S: Clinical global inventory-severity; GAS: Global assessment scale; OL: Open-label; PANSS: Positive and negative symptom scale; PDR: Physician's Desk Reference.

Table 2c. Finding of reports at use greater than PDR doses (olanzapine, open-label trials) (continued)

Type (n)	Diagnosis (age)	Dose (mg/day)	Results				Ref
			Change in BPRS	*PANSS total (positive/ negative)*	*CGI-S*	*Frequent adverse events (%)*	
OL (25)	Schizophrenia Treatment-refractory (32)	15 – 25 (64% at 25)	-13.9 36% positive treatment response	-24.3 (-4.9/-8.0)	-1.28 CGI-I (1,2) = 44%	Anxiety (36) Hallucinations (20) Delusions (16) Insomnia (12)	44
			PANSS positive	*PANSS negative*	*PANSS excitement*		
OL (43)	Schizophrenia Treatment-resistant (41.6)	10 – 40					46
		> 20	2.0	2.0	-0.02		
		< 20	0.1	0.0	-3.4		
			Hospital admissions/ patient	*Hospital days*	*CGI-S*	*Patients remarkable or definite improvement (%)*	
OL (25)	Schizophrenia Switch study (39.7)	29.8				Positive symptoms (76), Negative symptoms (48)	48
		Pre	1.32	1042	5.20		
		Post	0.39	258 (expected)	2.90		

AIMS: Abnormal involuntary movement scale; BPRS: Brief psychiatric rating scale; CGI-S: Clinical global inventory-severity; GAS: Global assessment scale; OL: Open-label; PANSS: Positive and negative symptom scale; PDR: Physician's Desk Reference.

Table 2d. Finding of reports at use greater than PDR doses (ziprasidone)

Type (n)	Diagnosis (age)	Dose (mg/day)	Results			Ref
			Change in QTc	*Change in HR*		
OL (48)	Schizophrenia, schizoaffective (> 18)	40 (ziprasidone)	4.5	3.2		70
		160 (ziprasidone)	19.5	5.8		
		320 (ziprasidone)	22.5	8.0		
		2.5 (haloperidol)	-1.2	1.1		
		15 (haloperidol)	6.6	0.6		
		30 (haloperidol)	7.2	1.2		
			Psychotic sx	*Affective sx*	*Anxiety sx*	
RR (31)	Varied: treatment-resistant (M:38.4 F:45.6)	% respond at 240 mg/day	25	27	22	71
	n = 10 at 240 mg/day n = 21 at 320 mg/day	% respond at 320 mg/day	50	60	30	

BPRS: Brief psychiatric rating scale; CGI-S: Clinical global inventory-severity; EPS: Extrapyramidal symptom; HR: Heart rate; OL: Open-label; PDR: Physician's Desk Reference; RR: Retrospective review.

Table 2d. Finding of reports at use greater than PDR doses (ziprasidone) (continued)

Type (n)	Diagnosis (age)	Dose (mg/day)	Results			Ref
			Correlation of improvement in affective and psychotic symptoms	*Correlation of improvement in anxiety and psychotic symptoms*	*Side effects (%)*	
RR (37)	Schizophrenia spectrum 30%, bipolar (1 and 2) 33%, major depression 28% (43.4)	13/37 at < 320, 21/37 at 320, 3/37 at 400;480	p = 0.003	p = 0.034	None (83), Sedation (8.1), Akathisia, restless legs (2.7)	72
			Adverse events (%)	*Ziprasidone*	*Haloperidol*	
RR (58)	Schizophrenia, schizoaffective (> 18)	30 (ziprasidone), 10 (haloperidol)	Somnolence	90.3	81.5	73
			Dizziness	22.6	7.4	
			Anxiety	16.1	7.4	
			Dry mouth	12.9	7.4	
			Nausea	12.9	7.4	
			EPS	6.5	33.3	
			Agitation	6.5	18.5	
			Insomnia	0	14.8	
				Ziprasidone	*Haloperidol*	
RR (132)	Nonorganic psychosis; 34.5 [Z], 32.8 [H]	5 – 20 mg q.i.d ziprasidone (3 days) 2.5 – 10 mg q.i.d haloperidol (3 days)	BPRS total	-6.24	-3.18	74
			BPRS agitation	-1.93	-0.80	
			CGI-S	-0.49	-0.15	
			Total adverse events	31.1%	50.0%	
			EPS	0%	21.4%	
			Dystonia	1.1%	7.1%	
			Hypertonia	0%	7.1%	
			Simpson-Angus	-0.61	3.80	
			Barnes akathisia	-0.03	0.44	
			Anticholinergic medication	14.4%	47.6%	
			QTc	+2.14 ms	+2.22 ms	

BPRS: Brief psychiatric rating scale; CGI-S: Clinical global inventory-severity; EPS: Extrapyramidal symptom; HR: Heart rate; OL: Open-label; PDR: Physician's Desk Reference; RR: Retrospective review.

adverse event was weight gain [46-48]. For example, one study found significant effects of the last week's mean dose (< 0.01) [46,47] and by doses > 20 mg/day (< 0.008 [46], < 0.05 [47]). EPS appears to have been further reduced at higher doses, with one exception [43]. Case reports, in general, showed minimal problems with adverse events. Other adverse events reported in case reports include reversible elevated QTc from 412 ms to 485 ms after 11 days of 40 mg/day [58] and increased PR interval to 227 ms and 230 ms after 4 and 2 weeks of 50 mg/day and 40 mg/day, respectively [59]. Long-term data in 8 patients taking olanzapine at 20 – 40 mg for 40 weeks [61] found weight gain in 87% with an average change of +8.0 kg. Other findings included an abnormally high average prolactin level (16.26 ng/ml, normal range 1.9 – 11.7 ng/ml).

3.3 Quetiapine

With regard to quetiapine, there have been no double-blind studies; however, results of two open studies [62,63], one

retrospective review [64], and five case reports [65-69] are available. The two open-label studies used maximum doses of 1400 mg/day and 1600 mg/day, respectively. The first was applied to patients having failed two previous antipsychotic trials, whereas the second was not. The first included a 3-week acute period, followed by an 11-week maintenance period; the second, a 4-week acute period followed by up to a 14-month maintenance period. Preliminary report of results of the first study showed an average dose of 1285.7 mg/day; no efficacy results were presented. The second study showed a 94% improvement by the CGI-I (improvement); hallucinations improved after only one week of therapy. In terms of safety parameters, there were no changes in EPS parameters in the two studies. Weight increased by a mean of 1.2 kg in the first study, but there was no significant weight change in the second. The first study showed a reduction in prolactin levels of 11.65 ng/ml. Neither study showed significant changes in laboratory values. Most commonly reported adverse events were: lethargy, orthostatic hypotension, dry mouth, headache and constipation.

A retrospective review in patients taking up to 2000 mg/day for 4 – 24 months, reported on marked improvement in psychopathology, sociability violence and behavioural disturbances. This was found in 4 out of 7 on monotherapy and 2 out of 7 on add-on therapy. However, 3 out of 7 patients had significant weight gain (39 – 70 lbs). With increased dose, an increased appearance of sedation, orthostatic hypotension and dysphagia were noted.

The five case reports include the following maximum doses: 2400 mg/day (1), 1800 mg/day (1), 1600 mg/day (1), 900 mg/day (1), and 1000 mg/day (1, a 12 year-old male). The adult responses were: a) 43 year-old with treatment resistant schizophrenia who after 2 – 3 weeks showed cessation of 'yelling, talking to himself and assaultive behaviour', b) a 34 year-old with schizophrenia who showed loss of weight on switch from olanzapine and full clinical remission; c) a 50 year-old with a long history of mania showed reduction in BPRS (91%) and YMRS (94%) over six weeks, d) a 48 year-old with chronic paranoid schizophrenia who did well on a dose of 2400 mg/day. Finally, a 12 year-old with the combined diagnosis of conduct disorder and attention-deficit hyperactivity disorder was placed on quetiapine because of lack of response and weight gain secondary to olanzapine. The patient improved and tolerated 1000 mg/day for 90 days. In terms of side effects, the only ones noted were: short-term (3 days) of moderate constipation and dizziness (1 out of 5), and urinary retention (in combination with 100 mg/day diphenhydramine) (1 out of 5).

3.4 Ziprasidone

Approved at doses up to 200 mg/day in schizophrenia, 160 mg/day in bipolar mania and 40 mg/day intramuscular, there is evidence for safe use up to 480 mg/day orally and up to 80 mg/day intramuscularly. There is one open study [70] and two retrospective chart reviews [71,72] on oral dosing. The open-label dose used doses of 40, 160 and 320 mg/day as well as haloperidol (2.5, 15 and 30 mg/day). Patients included were those with schizophrenia and schizoaffective disorder; focus was on potential adverse reactions. Findings showed a trend toward increasing heart rate of 3.2 (40 mg) to 5.8 (160 mg) to 8 (320 mg). However, this is not clinically meaningful. Mean QTc at the highest dose remained < 400 ms, although there was an increase of 22.5 ms from 160 mg/day (also not clinically significant). The most commonly reported side effects were somnolence, agitation, insomnia, headache; for haloperidol, they were somnolence, agitation, akathisia, EPS, insomnia and anxiety.

The two retrospective studies by the same authors had the same entry critieria: treatment resistance, incomplete response at 160 mg/day and minimal adverse events at 160 mg/day. The first review of mostly schizophrenia spectrum and bipolar patients reported on 10 patients at 240 mg/day and 21 patients at 320 mg/day, of which 15 showed improvement in psychosis on the Likert scale. The second group, at doses of up to 480 mg/day, included 51 patients including those meeting the following doses: bipolar 1 and 2 (33%), schizophrenia spectrum (30%), major depression (28%), other (8%). In the 37 patients treated at doses of ≥ 240 mg/day, there was a 58% improvement in psychotic symptoms, 53% improvement in affective symptoms and 34% improvement in anxiety symptoms. The first study showed no significant QTc changes with the most common side effect being sedation. Incidence of adverse events did not differ between those receiving 240 mg/day (3/10) and those receiving 320 mg/day (2/21, p = 0.29). Of course, if anything, the rate was decreasing. The second review also remarked on the lack of remarkable ECG results with no QTc results > 500 seconds. In terms of adverse events, again, it was found that sedation was one most frequently reported.

There have been three studies of intramuscular ziprasidone: one single-blind [73] and two open-label [74,75]. The single-blind study used doses of 20 and 30 mg, contrasting it to haloperidol (7.5, followed by 10 mg). In terms of QTc changes, results after the second injection were 12.8 ms for ziprasidone and 14.7 ms for haloperidol; change over 24 hours were less for ziprasidone (3.4 ms) than for haloperidol (6.3 ms). There were no QTc results > 500 ms. In terms of other adverse events, two stopped ziprasidone: EPS (1), hypotension and dizziness (1). However, three stopped haloperidol: EPS (2), increased depression and severe post-therapy psychosis (1). The first open-label study used up to 20 mg q.i.d of ziprasidone in contrasting it with up to 10 mg q.i.d haloperidol for 3 days. Ziprasidone showed better improvement over haloperidol in BPRS total ($p < 0.02$), BPRS agitation ($p < 0.015$) and CGI-S ($p < 0.002$) Ziprasidone was seen to have a slightly greater sedative effect at the last intramuscular (IM) assessment. In terms of measures of involuntary movements (Simpson-Angus rating scale, Barnes Akathisia scale, abnormal involuntary movement scale [AIMS]), patients taking ziprasidone showed improvements, whereas those taking haloperidol worsened. The second open-study comparison of ziprasidone and haloperidol showed dose-related improvement in BPRS, CGI-I, CGI-S, nurses

observation scale for inpatient evaluation. Blood levels for the 3 IM doses showed related increases in trough serum ziprasidone from 5 mg (8 ng/ml), to 10 mg (11 ng/ml), to 20 mg (25 ng/ml). Adverse events higher for ziprasidone were dizziness and pain at injection site, whereas for haloperidol, they were akathisia, EPS, dystonia and hypertonia. Changes in QTc were similar for the two compounds with none > 20% from baseline. As before, measures of abnormal movements improved with ziprasidone, but worsened with haloperidol.

3.5 Aripiprazole

This medication has been approved up to 30 mg/day and has a paucity of reports at use above that dose. There is one pharmacokinetic study [76] and one case report [77] available.

The pharmacokinetic study was conducted in 40 patients with stable schizophrenia or schizoaffective disorder. The paradigm was look at safety factor for 15 days at dose of 45, 60, 75 and 90 mg/day with a control group at 30 mg/day. Concentration of active metabolite was found to increase directly at each dose. There were no clinically significant changes in measures of abnormal movements (Simpson-Angus, Barnes akathisia, AIMS) with increased doses. Rate of the symptoms of akathisia and tachycardia showed higher incidence at the 90 mg/day dose. There were no significant changes in body weight or QTc (none reported at ≥ 500 ms). There were no changes in prolactin levels.

The case report is of 64 year-old with acute mania (with akinesia, tremor related to Parkinson's disease) switched from olanzapine and divalproex. On substitution of aripiprazole 40 mg/day for olanzapine, there was improvement in rapid speech, grandiose delusions with sexual preoccupation, flight of ideas, and increased psychomotor activity. Furthermore, there was improvement in the tremor and akinesia.

4. Expert opinion

The atypical antipsychotics, beginning with release of risperidone in 1995, have generally been approved (with the exception of risperidone) at doses that may not maximise their efficacy due to fears on increased problems with tolerance and safety.

Regarding risperidone, although approved for schizophrenia to 16 mg/day, it is only recommended to 8 mg/day because higher doses 'were not found more efficacious'. However, a review of the data shows that in the dose-ranging trial, the 10 mg/day dose performed worse (and had less associated EPS side effects) than the 6 mg/day results, which is not logical. It makes more sense to conclude that the results on 10 mg/day were flawed. Unfortunately, there were no reports on dosing > 6 mg/day. More testing is indicated at 16 mg/day, taking into account that one would expect higher levels of both EPS and prolactin.

Recommendation: with lack or minimal response, risperidone should be used up to a dose of 16 mg/day.

In terms of olanzapine, where PDR guidelines are a maximum 15 mg/day (schizophrenia) and 20 mg/day (mania), double-blind studies have employed doses up to 50 mg/day in patients with schizophrenia. However, at 25 mg/day, results were quite similar to chlorpromazine and clozapine. A dose of 40 mg/day in one extended 14-week trial showed only numerical benefit over higher than usual doses of risperidone (16 mg/day) and haloperidol (30 mg/day). A short-term cross-over study of 50 mg/day produced results that favoured clozapine over olanzapine. Open-label studies have generally used mean doses in the 20s. Although benefits are concluded, there are also reports of possible worsening of PANSS excitement and weight gain. Such symptom worsening may well militate against use of higher doses in bipolar mania or schizoaffective disorder, bipolar type. Although case reports using doses up to 80 mg/day are generally positive, as might be well expected, they also report on possible cardiovascular complications, including significant QTc elevations. Further, one should keep in mind that higher doses may also increase the risk for weight gain and associated problems with fasting blood sugar and hyperlipidaemia.

Recommendation: with lack or minimal response, olanzapine may show further clinical improvement to 30 mg/day. Doses up to 40 mg/day should be used with caution, particularly in bipolar disorder.

Quetiapine, which was approved for schizophrenia at a maximum of 750 mg/day and for mania at 800 mg/day, in open-label study results appears to frequently lead to further clinical benefit up to 1600 mg/day which was safe and well-tolerated. However, at doses of ≥ 2000 mg/day, the clinical benefit of quetiapine may be offset by increased risk of significant weight gain.

Ziprasidone's report incorporates two types of recommendations: IM and PO (per oral). The IM, currently approved at a maximum of 40 mg/day, has been successfully applied in controlled comparisons to haloperidol. A dose of up to 80 mg/day IM showed increasing dose-dependent improvement with less side effects than the comparator as well as a lack of QTc effects. Oral ziprasidone has been approved for use in schizophrenia to 200 mg/day and in mania at 160 mg/day. In the open-label and two retrospective chart reviews, doses up to 320 mg/day showed improved benefit at these higher doses in both schizophrenia and bipolar disorder without significant adverse events or QTc impact. More data are needed on higher doses.

Recommendation: with lack or minimal response, ziprasidone should be dosed IM up to 20 mg q.i.d. PO dosing with minimal respose should at least be dosed up to 320 mg/day.

Aripiprazole, with approval at 30 mg/day for both schizophrenia and mania, has the least available data because it is the most recently released atypical antipsychotic. One dose-ranging kinetic paper showed safety at 45, 60 and 75 mg/day, but increased tachycardia at 90 mg/day, and one case report showed benefit in treatment at a dose of 40 mg/day.

Recommendation: with lack or minimal response, dosing of aripiprazole up to 75 mg/day could be considered.

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75. Data on file, Pfizer, Inc.

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•• This safety study is important in showing the safety of aripiprazole up to more than twice normal – 75 mg/day orally, but with a caveat for further testing at 90 mg/day.

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Discontinuing Antidepressant Treatment in Major Depression

Adele C. Viguera, MD, Ross J. Baldessarini, MD, and Jonathan Friedberg, MD

Maintenance treatments in bipolar disorders and schizophrenia are securely established, and their discontinuation is associated with high but modifiable risk of early relapse. The benefits of long-term antidepressant treatment in major depression and the risks of discontinuing medication at various times after clinical recovery from acute depression are not as well defined. Computerized searching found 27 studies with data on depression risk over time including a total of 3037 depressive patients treated for 5.78 (0–48) months and then followed for 16.6 (5–66) months with antidepressants continued or discontinued. Compared with patients whose antidepressants were discontinued, those with continued treatment showed much lower relapse rates (1.85 vs. 6.24%/month), longer time to 50% relapse (48.0 vs. 14.2 months), and lower 12-month relapse risk (19.5 vs. 44.8%) (all $p <$ 0.001). However, longer prior treatment did not yield lower postdiscontinuation relapse risk, and differences in relapses off versus on antidepressants fell markedly with longer follow-up. Contrary to prediction, gradual discontinuation (dose-tapering or use of long-acting agents) did not yield lower relapse rates. Relapse risk was not associated with diagnostic criteria. More previous illness (particularly three or more prior episodes or a chronic course) was strongly associated with higher relapse risk after discontinuation of antidepressants but had no effect on response to continued treatment; patients with infrequent prior illness showed only minor relapse differences between drug and placebo treatment. (Harvard Rev Psychiatry 1998; 5:293–306.)

> *...if black blood issue forth, bleed on; if it be clear and good, let it be instantly suppressed, because the malice of melancholy is much corrected by the goodness of the blood. If the party's strength will not admit much evacuation in this kind at once, it must be assayed again and again.*
>
> —Robert Burton, *The Anatomy of Melancholy* (1652)[1]

Depression is one of the most common major psychiatric disorders and accounts for high rates of morbidity, substance abuse, family disruption, disability, medical comorbidity, and suicide.[2–6] In the United States short-term or lifetime prevalence of major depressive disorder has ranged from 5.2% to 17.1%,[2–4] with the highest rate found in the most recent survey.[4] Annual direct (treatment) plus indirect (disability and premature death) costs for depressive disorders in the United States alone total several tens of *billions* of dollars.[7,8] Timely diagnosis and adequate treatment of depression are therefore crucial challenges for contemporary medicine. Tendencies toward high rates of recurrence and sustained disability in major depression, particularly among persons with a past history of multiple episodes, are important factors in planning long-term treat-

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Original Article

Differential Relapse Following Cognitive Therapy and Pharmacotherapy for Depression

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• Patients successfully treated during a 3-month period with either imipramine hydrochloride pharmacotherapy, cognitive therapy, or combined cognitive-pharmacotherapy were monitored during a 2-year posttreatment follow-up period. Half of the patients treated with pharmacotherapy alone continued to receive study medications for the first year of the follow-up. All other patients discontinued treatment at the end of the acute treatment phase. Patients treated with cognitive therapy (either alone or in combination with medication) evidenced less than half the rate of relapse shown by patients in the medication–no continuation condition, and their rate did not differ from that of patients provided with continuation medication. It appears that providing cognitive therapy during acute treatment prevents relapse. Whether this preventive effect extends to recurrence remains to be determined.

(*Arch Gen Psychiatry.* 1992;49:802-808)

Advocates of the psychosocial interventions have long argued that psychotherapy provides stable gains that survive the termination of treatment and reduce subsequent risk.[1] Although ongoing continuation and maintenance medication are known to reduce risk,[2,3] there is no evidence that pharmacotherapy confers any protection against the return of symptoms after treatment has been terminated.[4] Since the majority of depressed individuals will experience multiple episodes, the capacity of an intervention to prevent the return of symptoms after treatment may be at least as important as its ability to treat the current episode.[5]

Can cognitive therapy reduce subsequent risk? Recent studies suggest that it might.[6] In a series of naturalistic follow-ups of controlled treatment trials, patients who had been treated with cognitive therapy showed approximately half the rate of posttreatment relapse than did patients who had been treated pharmacologically.[7-9]

See also p 774.

Nonetheless, these findings cannot be considered conclusive.[6] Samples have typically been small, nonresponders have sometimes been included,[8] ascertainment of relapse has sometimes relied on retrospective chart review[7] or infrequent (biannual) reevaluations,[9] and definitions of relapse have typically included return to treatment, even if it occurred in the absence of documentable distress. Finally, given that patients included in the follow-ups typically represented only a fraction of those initially assigned (patients must both complete and respond to treatment to be included), it is possible that cognitive therapy's apparent preventive effect results from an artifact. If pharmacotherapy is more likely than cognitive therapy to retain high-risk patients, then acute treatment could serve as a "differential sieve" that systematically biases the groups entering the follow-up. (We are indebted to an anonymous reviewer for suggesting and naming this possibility.)

In this article, we describe a 2-year follow-up of depressed outpatients treated in a controlled comparison of imipramine pharmacotherapy vs cognitive therapy, both singly and together. Our primary interest was in determining whether cognitive therapy prevents relapse after successful treatment. We also hoped to compare it with ongoing continuation medication, the current standard of treatment. Our study was designed before the publication of the naturalistic follow-ups just reviewed, and it shares many of the limitations of those earlier trials. Nonetheless,

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Read in part before the 141st Annual Meeting of the American Psychiatric Association, Montreal, Quebec, May 12, 1988.

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CPT Follow-up—Evans et al

Cognitive Therapy and Pharmacotherapy for Depression

Sustained Improvement Over One Year

Anne D. Simons, PhD; George E. Murphy, MD; Jeffrey L. Levine, PhD; Richard D. Wetzel, PhD

• Seventy patients with nonbipolar affective disorder who completed a 12-week course of either cognitive therapy (CT), pharmacotherapy, CT plus active placebo, or CT plus pharmacotherapy were assessed one month, six months, and one year after termination of active treatment. Of the 44 patients who had originally responded to treatment, 16 relapsed as defined by reentry into treatment or by self-reported depression scores in the moderately depressed range. Twenty-eight patients remained well during the one-year follow-up. Patients with relatively high levels of remaining depressive symptoms on completion of treatment relapsed more often than those who had little or no residual depression. Further, at treatment termination, patients who relapsed had significantly higher scores on a measure of dysfunctional attitudes. Patients who had received CT (with or without tricyclic antidepressants) were less likely to relapse in the one-year follow-up period than patients who received pharmacotherapy.

(*Arch Gen Psychiatry* 1986;43:43-48)

The episodic nature of affective disorder argues for research into the durability of the effects of treatment. The sustainment of improvement following termination of therapy, as well as acute effects, is important to the overall assessment of the costs and benefits of different treatments of depression. This question requires follow-up studies, research that is difficult due to a number of conceptual and methodologic issues. *Relapse* and *recurrence* typically refer to the reappearance of symptoms after symptom-free periods of variable length. *Relapse* typically refers to the return of the index episode and is applied when symptoms reappear after a short period of time. *Recurrence* refers to a new episode and is used when symptoms reappear after a longer period of time. Although these concepts presume recovery from the index episode, subsets of patients who remain symptomatic at the end of treatment have been included in frequency counts of relapse and recurrence, a practice that confuses rather than clarifies the question under study.

Follow-up studies have also suffered from the lack of generally accepted operational definitions of these different patient subgroups. Klerman[1] suggested a definition of *relapse* as the return of symptoms within six to nine months after the onset of the index episode, implying that the return of symptoms is part of the previous episode. He viewed *recurrence* as the return of symptoms after a symptom-free period of at least six to 12 months from the resolution of the previous episode, implying that these symptoms constitute a new episode. These definitions offer an approximate temporal framework for definitions of relapse and recurrence, but they do not state what constitutes the "return of symptoms." The return of symptoms can be defined by several sets of criteria, each with a corresponding set of problems. Two major criteria are diagnosis of major depression and return to treatment. Requiring sufficient symptoms for a rediagnosis of a major depressive episode avoids inflating relapse rates by not counting people experiencing normal bouts of low mood. However, unless assessment is frequent, briefer relapses will be missed.

Conversely, if return to treatment is used as the criterion, individual differences in help-seeking behavior potentially cause both overinclusion and underinclusion of cases. Patients whose symptoms may be severe but who are too demoralized to seek help are falsely excluded, while patients resuming treatment for problems not necessarily associated with depression (or for subsyndromal problems) constitute false positives. Any definition, therefore, must compromise between overinclusion and underinclusion of cases. The question under investigation may tip the balance in either direction. For example, the study of the long-term effects of specific treatments calls for a relatively stringent definition of remission to protect against false claims of the long-term power of any one modality.

Only a few studies have systematically attempted to

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Depression—Simons et al 43

Original Article

Course of Depressive Symptoms Over Follow-up

Findings From the National Institute of Mental Health Treatment of Depression Collaborative Research Program

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Joseph F. Collins, ScD; Paul A. Pilkonis, PhD; Edward Beckham, PhD; David R. Glass, PhD;
Regina T. Dolan, PhD; Morris B. Parloff, MD*

• We studied the course of depressive symptoms during an 18-month naturalistic follow-up period for outpatients with Major Depressive Disorder treated in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. The treatment phase consisted of 16 weeks of randomly assigned treatment with the following: cognitive behavior therapy, interpersonal therapy, imipramine hydrochloride plus clinical management (CM), or placebo plus CM. Follow-up assessments were conducted at 6, 12, and 18 months after treatment. Of all patients entering treatment and having follow-up data, the percent who recovered (8 weeks of minimal or no symptoms following the end of treatment) and remained well during follow-up (no Major Depressive Disorder relapse) did not differ significantly among the four treatments: 30% (14/46) for those in the cognitive behavior therapy group, 26% (14/53) for those in the interpersonal therapy group, 19% (9/48) for those in the imipramine plus CM group, and 20% (10/51) for those in the placebo plus CM group. Among patients who had recovered, rates of Major Depressive Disorder relapse were 36% (8/22) for those in the cognitive behavior therapy group, 33% (7/21) for those in the interpersonal therapy group, 50% (9/18) for those in the imipramine plus CM group, and 33% (5/15) for those in the placebo plus CM group. The major finding of this study is that 16 weeks of these specific forms of treatment is insufficient for most patients to achieve full recovery and lasting remission. Future research should be directed at improving success rates of initial and maintenance treatments for depression.

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Numerous studies have investigated the efficacy of standardized, short-term psychotherapeutic treatments for outpatient, nonbipolar depression.[1] The most well known of these treatment approaches include cognitive behavior therapy (CBT),[2] interpersonal therapy (IPT),[3] and a variety of behavioral treatment approaches.[4-7] Efficacy has been reported for these treatments by findings of no differences or superior outcome compared with standard antidepressant medication conditions or superior outcome compared with a variety of control conditions. The National Institute of Mental Health Treatment of Depression Collaborative Research Program (TDCRP), a multisite collaborative study, investigated the efficacy of CBT and IPT in comparison with a standard reference condition of imipramine hydrochloride plus clinical management (CM) and pill placebo plus CM for the treatment of outpatients with Major Depressive Disorder (MDD).[8] Outcome findings for depressive symptoms and general functioning at termination of treatment have been reported.[9] Very briefly, in the treatment phase no significant differences were found between either of the psychotherapies and imipramine plus CM at termination from treatment; however, imipramine plus CM showed an advantage in its more rapid effects.[10] Short-term results also provided some evidence for the efficacy of IPT compared with placebo plus CM in terms of recovery, although the findings for IPT were less consistent than for imipramine plus CM. For those patients who were more severely depressed and functionally impaired at pretreatment, there was some evidence of the efficacy of IPT and strong evidence of the efficacy of imipramine plus CM. With regard to CBT, although patients improved nearly as much as the patients who underwent IPT, there was an absence of sig-

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Depressive Symptoms—Shea et al

Cognitive-Behavior Therapies for Major Depression: Current Status with an Emphasis on Prophylaxis†

Brian F. Shaw, Ph.D.*

This paper reviews the major findings of studies evaluating the efficacy and secondary prevention aspects of the cognitive-behavior therapies (CBT) for depression. Currently, CBT includes well-developed systems of several psychotherapy/behavior therapy in both individual and group modalities. These approaches have been shown to be efficacious, when comparable to any standard treatment, with unipolar, non-psychotic depressions. They remain untested in bipolar disorders. The paper addresses both values of combined treatments, and the limitations of these approaches. As the Beck, Rush, Shaw and Emery (1979) approach to CBT has been shown in seven studies to lower relapse and recurrence rates, these important findings are emphasized. The paper is placed in the context of the literature of psychosocial factors in the onset, maintenance and recurrence of the depressive disorders.

INTRODUCTION

The recent literature examining the follow-up status of depressed patients treated 1 to 2 years previously with cognitive-behavior therapy reveals a potential prophylactic effect. This finding, if confirmed in other studies with controlled designs, will be an important development in the treatment of depression. It will be encouraging sign for this class of psychotherapy. Furthermore, if the clinician considers combining pharmacotherapy with cognitive-behavior therapy during the acute phase of major depression, we will have a reasonably powerful treatment. We will have a hope of reducing the rate of relapse in this recurring disorder.[27] This paper will review the findings that lead to this conclusion. It will also discuss some of the psychosocial vulnerability factors associated with major depression.

Recently two well-written chapters have reviewed the current status of cognitive-behavior therapy in clinical outcome trials.[22,46] Many of the studies described in these chapters form the database for the current paper, which, with the benefit of several other investigations, will emphasize the relapse and recurrence problem in major depression. The evidence of efficacy of cognitive-behavior therapy in the acute episode of unipolar, major depression is strong. The issues of comparative efficacy and the specific effects of treatment compared with nonspecific, supportive intervention is less clear.

COGNITIVE-BEHAVIOR THERAPIES

The cognitive-behavior therapies are a group of short-term, active and directive treatments that emphasize increasing activity, (behavior), with careful work on the cognitive, thinking, perception, aspects of the patient's experience. They meet the criteria for systems of psychotherapy[15] in that they are based on a theory of behavior change, an empirical literature testing the central constructs and reasonably well-defined treatment manuals. The most widely studied method was proposed by Beck et al,[2] although other related forms of treatment including Lewinsohn's[31] psychoeducational, behavioral program and Rehm's[38] self-control therapy have also been reasonably well investigated.

Cognitive-behavior therapy[2] is designed as a short-term treatment with therapy typically lasting 15-25 sessions over 4-6 months. The goal of cognitive therapy is to teach the patient how to cope with the symptomatic changes associated with depression by identifying and challenging negatively-distorted cognitions about the self, the world, and the future i.e., hopelessness. The preventive aspect of the therapy is presumed to be the alteration of dysfunctional attitudes. Most of these associate self-worth with the approval of specific others and/or the achievement of certain goals that leave the person emotionally vulnerable to loss events. Related cognitive approaches include rational-emotive therapy,[13] rational restructuring[17] and self-instructional therapy.[33] However, these methods have not been widely evaluated with depressed patients per se.

Self-control therapy[38] is a short-term (approximately 20 sessions) approach involving self-monitoring, self-evaluation and self-reinforcement. The conceptualization of depression emphasizes the individual's selective attention to negative life experiences, the demand of excessively high standards, and a pattern of little self-reinforcement.

Lewinsohn's[30] approach, while also goal-oriented and focussed, is more behavioral in its emphasis. It is based on the notion of reinforcement and strives to teach patients how to obtain more positive interactions with the environment, particularly through the scheduling of positive

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Relapse After Cognitive Behavior Therapy of Depression: Pot
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pg. 1046

Relapse After Cognitive Behavior Therapy of Depression: Potential Implications for Longer Courses of Treatment

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Objective: The authors studied the risk of relapse among depressed patients after cognitive behavior therapy in order to document the need and potential indications for longer-term models of treatment. Method: Forty-eight patients with major depression who responded during a 16-week course of cognitive behavior therapy entered a 1-year prospective follow-up study, as did two patients who received 20 weeks of therapy. Standardized, independent clinical assessments were completed 1, 3, 6, 9, and 12 months after treatment. Relapse was defined as, at minimum, a 2-week period in which the subject met the DSM-III-R criteria for major depression and had a Hamilton depression scale score of 15 or more. Results: Sixteen patients (32%) relapsed during the 1-year follow-up. Correlates of relapse included a history of depressive episodes, higher levels of depressive symptoms and dysfunctional attitudes, slower response to therapy, and being unmarried. Patients who fully recovered during therapy (Hamilton depression score of 6 or less for 8 weeks or more) were at significantly lower risk for relapse than those who partially recovered (9% and 52%, respectively). Slower response to therapy, unmarried status, and high residual scores on the Dysfunctional Attitudes Scale were independently and additively related to increased risk of relapse. Conclusions: These findings provide further evidence of a relation between residual symptoms and relapse after cessation of active treatment. The authors strongly recommend that models of longer-term psychotherapy be developed for depressed patients who do not recover fully during time-limited cognitive behavior therapy.

(Am J Psychiatry 1992; 149:1046–1052)

A number of studies over the past 15 years have indicated that cognitive behavior therapy (1) is an effective short-term outpatient treatment of depression (2). Indeed, there is some suggestion that an initial, time-limited course of cognitive behavior therapy may convey additional prophylactic benefits after termination of therapy (3–7). Nevertheless, relapse after termination of acute treatment of depression remains a significant public health problem (8, 9), and, more specifically, the maintenance of therapeutic gains after short-term cognitive behavior therapy is far from complete (3–7). We therefore initiated a prospective, longitudinal study of patients who had been treated with cognitive behavior therapy in the Psychobiology of Recovery in Depression project (10, 11). One goal of the longitudinal study was to document the frequency of relapse during the first year of follow-up as a way of determining whether there is a need for developing longer-term models of cognitive behavior therapy. A second goal was to identify clinical correlates of relapse that might help clinicians to identify patients who would be likely to benefit from such continued therapy. We now report the 1-year outcome and clinical correlates of relapse in a study of 50 patients who responded during time-limited cognitive behavior therapy.

METHOD

The recruitment, screening, assessment, and treatment of outpatients participating in the Psychobiology of Recovery in Depression project protocol have been described in detail elsewhere (10, 11). To summarize briefly, patients were initially evaluated by a team of

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How long to onset of antidepressant action: a meta-analysis of patients treated with fluoxetine or placebo

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The onset of action of antidepressant medications is commonly believed to require three or more weeks based on clinical observation and corollary receptor-based hypotheses. However, this is not congruent with early published observations with the tricyclic antidepressants and has been recently challenged. Time to response has implications for treatment compliance, dose adjustment, patient well-being, and the associated economic costs of depression. Weekly improvement on the 21-item Hamilton Depression Rating Scale ($HAMD_{21}$) from baseline and time to response for fluoxetine- and placebo-treated patients were compared. Data from six double-blind clinical trials of 6-7 weeks' duration, in which 1447 patients with DSM-III-R major depression had been randomly allocated to fluoxetine (n = 962) or placebo (n = 485), were pooled. Analysis of variance was used to evaluate $HAMD_{21}$ improvement and the Kaplan-Meier estimate was used to evaluate time to response (≥ 50% improvement in $HAMD_{21}$). Improvement in $HAMD_{21}$ was statistically significantly greater for fluoxetine than placebo beginning at Week 1 and continuing throughout all weeks of therapy. However, Week 1 and 2 results varied among the individual studies. HAMD factors of cognition and psychomotor status revealed the most rapid changes for fluoxetine-treated compared with placebo-treated patients. The probability of achieving a clinical response, defined as a $HAMD_{21}$ score reduction from baseline of at least 50%, was similar for both fluoxetine (0.043) and placebo (0.049) at the end of Week 1. However, by Week 2 and thereafter the probability of a response was greater for fluoxetine than placebo. These results challenge the current belief that a 3 to 4 week delay in the onset of antidepressant action is to be expected. Alternatively, response to pharmacotherapy is likely incremental, and the rate of response highly individualized. More detailed attention to patient heterogeneity and early response patterns is encouraged.

Keywords: Antidepressant response – Fluoxetine – Onset of action

INTRODUCTION

With the introduction of tricyclic antidepressant (TCA) pharmacotherapy in the 1960s, and later the selective serotonin uptake inhibitors (SSRIs), a quantum advance in depression treatment outcome was realized. However, many aspects of antidepressant response remain unknown. One important example is the presumed time delay between the initiation of an antidepressant and the onset of clinical improvement. Experience from large-scale, multi-center, controlled trials suggest that a statistically significant separation from placebo may require several weeks or more of therapy (George and Lydiard, 1991). One possible explanation for a delayed response has been the prerequisite time for induction of one or more receptor-based modifications (Charney *et al.*, 1981). Such changes (e.g. down-regulation) are believed to require a period of adaptation following the initial introduction of an antidepressant (Stahl, 1992). Some authors further believe that achievement of a steady state therapeutic dose is prerequisite to this adaptation (Lydiard *et al.*, 1984; Khan *et al.*, 1989). Such receptor-based hypotheses have been interwoven with mean baseline to endpoint efficacy group comparisons to placebo in support of the belief that antidepressant medications require several weeks or more "to begin to work" (Stassen *et al.*, 1993). However, this concept of therapeutic latency stands in stark contrast to the original observations with imipramine reported by Kuhn (1957). Several authors, most notably Angst, have suggested the concept of antidepressant latency to be "something of a myth" (Angst, 1970).

If this concept were to be valid, therapeutic latency would have obvious disadvantages. Patient pessimism, already inherent in depression, would be prolonged. Compliance would likely be compromised. The economic consequences, both direct and indirect depression-associated expenses, would be magnified by each week the treatment response is delayed.

Recently Bowden and colleagues reported results from a 6 week double-blind, parallel study of 58 major depressed patients randomized to either fluoxetine or imipramine (Bowden *et al.*, 1993). Improvement on the Hamilton Depression Rating Scale (HAMD; baseline score to last observation) was statistically significant for both treatment groups beginning with Week 1. This led to their conclusion that "steady state pharmacokinetics are not requisite for the early clinical efficacy of fluoxetine." However, a limitation in the study design was that both subjects and raters knew that randomization would be to an active antidepressant.

In the following report a large series of blinded, placebo-controlled trials of fluoxetine were analyzed to both replicate the conclusion that steady state concentrations are not mandatory for response and to characterize onset of action patterns relative to placebo.

METHODS

Data sources and design

Data were evaluated from six United States Investigational New Drug single- and multi-center, randomized, double-blind, placebo-controlled fluoxetine clinical trials in major depression (Trials HCAC, HCCH, HCCJ, HCCP, HCDD and HCAF). The trials included 1447 patients (fluoxetine $n = 962$, placebo $n = 485$). Fluoxetine doses ranged from 20 to 80 mg/day, except in one trial in which the range was 5-40 mg/day. In four trials, fluoxetine doses were individually adjusted; in two trials patients were randomly assigned to one of several fixed doses. One trial compared fluoxetine with placebo and a tricyclic antidepressant. Only patients treated with fluoxetine or placebo were included in this analysis. Trials lasted either 6 or 7 weeks; in each a 1-week placebo lead-in period preceded 5 or 6 weeks of double-blind therapy. Assessments were conducted at approximately weekly intervals.

Study population

Subjects met criteria for non-psychotic major depressive disorder [one trial used Research Diagnostic Criteria (Spitzer *et al.*, 1984), four trials used *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-III criteria (American Psychiatric Association, 1987), one trial used DSM-III criteria but required that symptoms had persisted for at least 1 month's duration]. In five trials, subjects were further required to exhibit a baseline score $\geqslant 20$ on the 21-item Hamilton Rating Scale for Depression ($HAMD_{21}$; Hamilton, 1960). One trial included patients with either mild depression ($HAMD_{21}$ score of 15-19) or moderate depression ($HAMD_{21}$ score $\geqslant 20$). However, the mildly depressed patients were not included in this analysis. If an individual's screening $HAMD_{21}$ total score improved by 20% or more or fell below 20 during a 1 week placebo lead-in period, they were discontinued prior to randomization.

Statistical methods

All tests of hypotheses on main effects were conducted at a two-sided $\alpha = 0.05$ level while interaction effects were tested at the $\alpha = 0.10$ level. If a statistically significant treatment-by-study interaction was present, a summary of the results for each study was given. No adjustments for multiple comparisons were made.

The categorical demographic variable gender was evaluated using the chi-square test with one degree of freedom. Results were obtained from PROC FREQ in SAS (SAS, 1989). Age at baseline was ranked then analyzed by fitting the linear model containing the terms treatment, investigator and the treatment-by-investigator interaction. PROC RANK and PROC GLM (type III sums of squares) in Version 6 of SAS were used (SAS, 1989).

Proportions of fluoxetine-treated and placebo-treated patients that completed the study or discontinued for lack of efficacy, an adverse event, or all other reasons were compared using the Cochran-Mantel-Haenzel statistic stratified by study (Cochran, 1954; Mantel and Haenzel, 1959). The results were obtained from PROC FREQ in SAS (SAS, 1989). Heterogeneity among the results from the studies was evaluated using the Breslow-Day statistic (Breslow and Day, 1980). The chi-square test with one degree of freedom was used to analyze results by study when heterogeneity was present.

Discontinuation for lack of efficacy by Weeks 1 and 2 of therapy were analyzed similarly.

At each week, changes in $HAMD_{21}$ total scores from baseline were ranked and then analyzed for treatment differences by fitting a linear model described above. Least squares means are presented because of an imbalance in the number of patients receiving fluoxetine relative to placebo in two of six studies. All patients with a baseline and at least one post-baseline measurement were included in the efficacy analyses. Change scores were defined as the score at a given visit minus the baseline score. Last week carried forward change scores are presented unless otherwise noted. The HAMD factors (anxiety, cognitive disturbance, psychomotor retardation, sleep disturbance) were similarly analyzed (Cleary and Guy, 1975).

The Kaplan-Meier estimate was used to evaluate the difference between the distribution of the week of response and remission for the two treatment groups (Kaplan and Meier, 1958). Response was defined as a reduction greater than or equal to 50% for both $HAMD_{21}$ total and a core item group of depressive signs and symptoms (items 1-3, 7, 8, 14-17). If a patient's $HAMD_{21}$ total score was less than or equal to 8, the patient was classified as a remitter. The corresponding Wilcoxon test (power to detect differences early) and log rank test (power to detect differences

TABLE I. Baseline and weekly last-week-carried-forward change in $HAMD_{21}$ total

Week of therapy	HAMD total	Fluoxetine ($n = 930$)		Placebo ($n = 468$)		p values[1]	
		Least squares mean	Standard error	Least squares mean	Standard error	Treatment	Treatment-by-project
0	Baseline	25.5	0.24	25.5	0.27	0.740	0.827
1[2]	Change	−5.7	0.30	−4.6	0.34	0.016	0.054
2[3]	Change	−8.1	0.36	−6.5	0.41	0.003	0.087
3	Change	−9.7	0.41	−7.4	0.46	<0.001	0.234
4	Change	−10.5	0.44	−8.0	0.49	<0.001	0.360
5	Change	−11.3	0.46	−8.3	0.51	<0.001	0.474
6	Change	−11.7	0.47	−8.3	0.53	<0.001	0.577

$HAMD_{21}$ = 21-item Hamilton Rating Scale for Depression.

[1] Rank change analyzed.

[2] Fluoxetine $n = 916$, placebo $n = 457$.

[3] Placebo $n = 467$.

late) were used to test for differences between the two distributions (Kalbfeisch and Prentice, 1980).

RESULTS

Between the 962 subjects randomized to fluoxetine and the 485 to placebo, no significant differences were noted at baseline for age (39.2 ± 12.3 years, mean ± S.D.) or gender (61% female). As shown in Table I, there were also no statistically significant $HAMD_{21}$ baseline differences between fluoxetine-treated and placebo-treated patients. Overall 59% of the fluoxetine-treated and 49% of the placebo-treated patients completed the study. Table II summarizes the various reasons for premature discontinuation. Further evaluation of discontinuation for lack of efficacy revealed that the difference in proportions of fluoxetine-treated and placebo-treated patients that discontinued by Week 1 of therapy was not statistically significant (fluoxetine 0.6%, placebo 1.4%; $p = 0.179$). However, by Week 2 of therapy 13.6% of the placebo-treated patients vs 4.2% of the fluoxetine-treated patients had discontinued for lack of efficacy. This difference was statistically significant ($p < 0.001$). Of note, heterogeneity was observed among the individual studies. In one study, no patients discontinued by Week 2 of therapy for lack of efficacy. In four of the six studies, a greater proportion of placebo-treated patients discontinued by Week 2 of therapy for lack of efficacy (one study showed statistical significance), while in one study there was a greater proportion of fluoxetine-treated patients that discontinued by Week 2 of therapy for lack of efficacy.

TABLE II. Patient disposition by treatment group

Disposition	Fluoxetine ($n = 962$)		Placebo ($n = 485$)		p value[1]
	n	%	n	%	
Completed the study	566	58.8	237	48.9	0.001
Discontinued					
Adverse event	132	13.7	21	4.3	<0.001
Lack of efficacy	133	13.8	167	34.4	<0.001[2]
Other[3]	131	13.6	60	12.4	0.527

[1] Cochran-Mantel-Haenszel statistic.

[2] A greater proportion of placebo-treated patients discontinued in all of the studies for lack of efficacy. The result was statistically significant in three of the six studies.

[3] Consists of lost to follow-up, patient or physician decision, entry criteria not met and protocol variance.

As is evident in Table I, beginning at Week 1 and continuing during all weeks of therapy, fluoxetine was statistically significantly more effective than placebo in $HAMD_{21}$ total score change (last week carried forward analysis). Two methods (last visit carried forward and observed cases) of analysis were employed to minimize a possible effect by premature study discontinuations. Of note, the mean decreases at each week were numerically greater in the observed cases analysis. A treatment-by-study interaction was statistically significant at Weeks 1 and 2. At Week 1, the mean change in $HAMD_{21}$ total score favored fluoxetine in three of the six studies (one statistically significantly) and favored placebo in three of the studies (none statistically significantly). At Week 2, the mean change in $HAMD_{21}$ total score favored fluoxetine in five of the studies (one statistically significantly) and favored placebo in one of the studies. A parallel analysis of the weekly observed change in $HAMD_{21}$ scores demonstrated very similar results again favoring fluoxetine from Week 1 on.

A third analysis of weekly change from baseline on the $HAMD_{21}$ factors (Cleary and Guy, 1975) was conducted to test if a differential response pattern existed among the individual clusters. A statistically significant improvement favoring fluoxetine from Week 1 on for the cognitive disturbance and psychomotor retardation factors was seen ($p < 0.05$). A treatment-by-study interaction was

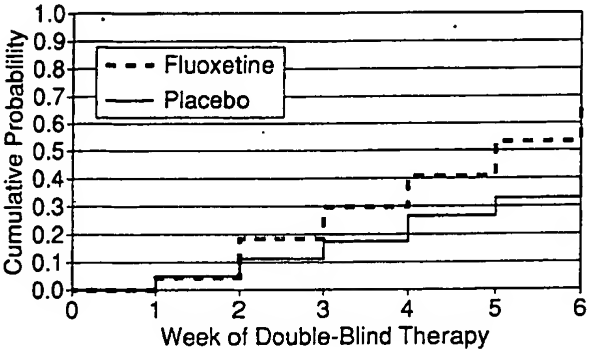

FIG. 1. Cumulative probability of response by week of double-blind therapy.

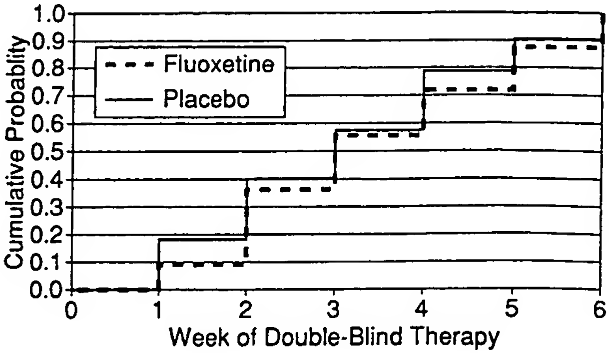

FIG. 2. Cumulative probability of response by week of double-blind therapy for patients that responded.

statistically significant at Weeks 1 and 2 in the analysis of the psychomotor retardation factor. At Weeks 1 and 2, mean change in the retardation factor favored fluoxetine in the same four of six studies (one statistically significantly) and favored placebo in two studies (one statistically significantly). The anxiety/somatization cluster numerically favored fluoxetine from Week 1 on and achieved statistical significance at Week 3. The factor of sleep disturbance numerically favored fluoxetine beginning at Week 2 and achieved a statistically significant separation by Week 6.

Figure 1 portrays the distributions of the week in which a clinical response was achieved for the fluoxetine-treated group and the placebo-treated group. (All patients) A difference in the distributions is evident from the second treatment week on favoring fluoxetine. Wilcoxon and log rank tests were significant ($p < 0.001$). Remission data (not shown), as defined in Methods, revealed a similar pattern. However, the criterion for remission is more severe, thus the probability of achieving remission was lower at each week. Significant separation in the remission patterns was first seen at Week 3 favoring fluoxetine. In order to exclude adverse events (e.g. sedation) as having influenced $HAMD_{21}$ response, a separate analysis of response based on core depressive signs and symptoms was also conducted. These items (1, 2, 3, 7, 8, 14, 15, 16, 17) provided even more robust evidence of a fluoxetine separation from placebo commencing with treatment Week 1 and continuing thereafter. An additional analysis (Kaplan-Meier) of responders only was carried out (Fig. 2). Of interest, the temporal pattern and proportions of those achieving and maintaining a response between fluoxetine and placebo revealed little meaningful difference throughout the 6 weeks of study. It should be noted that the responders' criteria used in the Kaplan-Meier method are more stringent than by analysis of variance, the former requiring a 50% or greater response which is also maintained for all subsequent patient visits. It is likely that more fluoxetine than placebo patients also achieved a modest level of improvement (25-49%) resulting in a greater group mean improvement by ANOVA.

DISCUSSION

In this series of placebo-controlled, double-blind trials the onset of action of fluoxetine significantly separated from placebo by the first week of post-randomized treatment. This differentiation, based on either the $HAMD_{21}$ total score or depression core symptomatic changes, was maintained throughout the 6 week study. The time-to-response analysis revealed that statistically significant treatment separation began at Week 2 and favored fluoxetine. A clinically significant separation beginning at Week 3 occurred for remission. A time course of response among four $HAMD_{21}$ factors revealed some differentiation, e.g. an earlier and more robust fluoxetine response relative to placebo emerged on the cognition and retardation factors. This suggests that differing symptom clusters in depression may respond relatively independent of one another. However, one caveat in the analyses of subfactors is that the potential for score change in an individual factor was less than that with the total $HAMD_{21}$ score change and thus, the ability to detect statistically significant differences may have been reduced. In the future, more frequent evaluation of such outcome measures early in the course of pharmacotherapy would be beneficial in this type of analysis.

Several published trials of fluoxetine and an active TCA comparator have shown fluoxetine to have an earlier or comparable onset of activity (Bowden *et al.*, 1993). However, in the direct comparison of two active agents, the results may be biased by an "expected" response on the part of clinical raters, i.e. all randomized subjects will receive active treatment. An alternative design is to include a placebo arm. This permits observation of the

natural course of depression independent of an active pharmacologic component while reducing rater expectations. However, even a placebo-controlled trial may obscure detection of an early onset of antidepressant activity. Quitkin *et al.* (1991) characterized the pattern of onset/offset of placebo response in 263 controlled clinical trial participants with major depression and/or dysthymia over 6 weeks. The early patterns of response between drug (mianserin, several tricyclic antidepressants, tranylcypromine, and phenelzine) and placebo were similar. However, the authors reported that "abrupt improvements", i.e. in the first 2 weeks, were less likely to persist. In this present study the course of placebo improvements was parallel to those seen with fluoxetine (see Fig. 2). However, the Kaplan-Meier analysis revealed a significantly greater number of early responders were receiving fluoxetine. This argues against Quitkin *et al.*'s premise that specific drug effects are unlikely in the first 2 weeks of therapy. Of note, those investigators did caution that "onset may be earlier or later than two weeks depending on dose, rate of absorption, diagnosis, and other variables." At least with the available fluoxetine data in this trial, both early abrupt and gradual responses were seen and appeared to persist relative to placebo.

While the literature suggests that the onset of placebo or drug response follows a similar course among non-responders, it seems probable that placebo subjects are less likely to remain in a trial. Stassen and colleagues conducted a meta-analysis of 429 major depressed subjects treated with either amitriptyline, oxaprotiline or placebo for 5 weeks (Stassen *et al.*, 1993). These investigators reported an earlier rate of premature trial discontinuations among placebo assignees. Fifty per cent of dropouts occurred in the first 8 days among placebo subjects vs 40% at 12 days for those on active therapy. The authors suggest that lack of effect with placebo was the principal reason for early discontinuations. In contrast, those assigned to active treatment were more likely to have discontinued due to adverse events. Our overall findings corroborate a higher/earlier incidence of early discontinuations among those assigned to placebo. In the current study 14% of the placebo-treated patients and 2% of the fluoxetine-treated patients terminated due to a lack of effect within the first two study weeks. Perhaps the early onset of symptomatic improvements (e.g. a favored cluster of HAMD items) or mild adverse event experiences sustain antidepressant compliance among those assigned an active therapy in contrast to placebo study subjects. In summary, data from the present study paralleled the findings of Stassen *et al.* (1993) and suggest that placebo assignees are more likely to discontinue early due to a lack of effect.

George and Lydiard (1991) reviewed 24 double-blind, placebo-controlled studies comparing fluoxetine or buproprion and failed to find evidence of a more rapid onset of action relative to conventional antidepressants. In their literature review they advised careful attention to response definition used, the effect of differential dosing, early improvement in certain rating factors that may actually represent drug side effects, e.g. sedation, and non-random patient distributions. The nature of the study design, dose and analysis of the core depressive signs and symptoms used in this current study attempted to address those concerns.

Bowden *et al.* (1993) investigated 58 major depressed patients who were randomized to either fluoxetine or desipramine for 6 weeks. Improvement on the HAMD total from baseline (last observation carried forward) was highly significant for both treatments from Week 1 on. Week 3 HAMD item 1 (mood change) was predictive of overall response at 6 weeks for fluoxetine only. The present study confirms Bowden and colleagues' view that early onset of response with fluoxetine is independent of steady state plasma concentration. Like fluoxetine, its major metabolite norfluoxetine is both a potent and selective serotonin uptake inhibitor which likely contributes to overall efficacy (Wong *et al.*, 1975). Fluoxetine has a half-life of 1-3 days, whereas that of norfluoxetine is 7-9 days. Thus, an estimate of the requisite time to achieve steady state would be 5-15 days for the parent and 35-45 days for norfluoxetine. While achievement of a steady state fluoxetine concentration by 1 week is possible in some subjects, it is not a likely explanation for the group results reported here. When coupled with the paucity of evidence supporting a fluoxetine plasma concentration:response relationship (Norman *et al.*, 1993), the early onset of clinical benefits was likely independent of attaining steady state.

Increasing evidence suggests that major depression is a heterogeneous syndrome and thus, a variable pattern of symptomatic improvement should be expected. Further efforts to characterize patterns or profiles of earlier responders versus a late or absent response is highly encouraged. Such a model would help determine appropriate dosing adjustments and importantly, patient expectations. In parallel, further characterization of placebo response has substantial importance for future clinical trials. Lastly, defining the time frame of individual response would be welcomed as a potential guideline to help reduce depression-associated health care expenses.

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The timing, specificity and clinical prediction of tricyclic drug effects in depression

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SYNOPSIS This research was aimed at studying the rate of action of tricyclic drugs in depressive disorders, specifying the behavioural effects associated with recovery, and predicting clinical response. The research design involved comparison of a recovered group with a group treated for the equivalent four weeks, who showed minimal to no response. The findings indicated significant differences in baseline characteristics between responders and non-responders. Further, the drugs were found to act early in the responders, within the first week of treatment. Specific changes at one week which distinguished responder and non-responder groups occurred in the disturbed affects, and in cognitive functioning. Improvements also occurred in somatic symptoms, but these latter changes were general and not associated with later recovery. At 2½ weeks, all facets of the depressed condition showed positive change in the responders. Implications of the results for assessing rate of tricyclic drug actions, their effects on the interaction of affect and neurochemistry, and the practical application of the results for the clinical situation, are discussed.

INTRODUCTION

This study, part of the National Institute of Mental Health-Clinical Research Branch Collaborative Program on the Psychobiology of Depression Biology Study (Katz *et al.* 1979; Maas *et al.* 1980; Secunda *et al.* 1980) was aimed at clarifying the timing of action and the specific effects associated with response to tricyclic drugs, issues basic to the understanding of their mechanisms of action in severely depressed patients.

Although there is an extensive literature dating from the late fifties on their overall clinical efficacy (Klerman & Cole, 1965; Medical Research Council, 1965; Davis *et al.* 1968; Kessler, 1978), there is little evidence on the timing and nature of the initial actions of the tricyclics on behaviour and affect. Imipramine and amitriptyline, and most widely used tricyclics, have clearly been established as effective treatments (when compared with placebo) for severe depressive disorders, resulting in recovery in approximately 50%, and in recovery or marked improvement in 65% of cases (Davis *et al.* 1968; Klerman & Cole, 1965).

Although there are some differences in the type of side effects the two drugs are reported to produce, and in their effects on neurotransmitter systems, only marginal differences have so far been found in their effects on behaviour and affect in depression (Kessler, 1978; Hollister *et al.* 1964). There is evidence that the tricyclic drugs act on somatic symptoms following the first week of treatment (DiMascio *et al.* 1979),

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and that improvements within the first two weeks can predict later recovery (Coryell *et al.* 1982). The consensus from such studies is, however, that early changes which signal later clinical response do not appear before two weeks of treatment.

Despite the importance of such information for understanding mechanisms of action, e.g. the interaction of drugs and neurotransmitter systems in depression, and for predicting clinical response, little hard evidence has been provided on when the tricyclics begin to act, or on the nature of the effects on emotion and behaviour which occur first in the recovery process. Investigations aimed at separating the drugs' initial actions on behaviour from those effects which appear later have been impeded by the nature of the recovery process itself. Once improvement begins, the process tends to move very rapidly. Any early specific effects the drugs may have appear to merge quickly or be integrated into the overall process. The drugs then appear to act equally on all aspects of pathology. Thus, identifying those specific drug actions on behaviour and affect which actually initiate the recovery process is difficult.

To examine further the issues of timing and specificity, data from this study were used to:

(1) determine in those patients who will respond when, at the earliest, changes in affect and behaviour can be discerned;

(2) identify the nature of tricyclic drug actions on behaviour and emotions which apparently initiate or are part of the recovery process;

(3) determine whether the early effects on symptoms and behaviour are of sufficient magnitude to be of practical, predictive value in the clinical situation.

METHOD

The rationale, research design and methodology of the Collaborative Program have been presented in detail in several reports (Katz *et al.* 1979; Maas *et al.* 1980; Secunda *et al.* 1980). A brief description of the study sample and the design follows.

Sample

Hospitalized patients with a diagnosis of primary major depression were assigned to the study following application of the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott & Spitzer, 1978), and the Research Diagnostic Criteria (RDC) (Spitzer *et al.* 1978). The programme was conducted across six US hospital centres (see acknowledgments). A total of 85 unipolar depressives (39 males and 46 females), and 47 bipolar depressives (31 males and 16 females) were studied. The mean age for the unipolars was 49·2, the bipolars 43·6, and the normal healthy controls, 45·8.

The patient sample was as a whole, severely ill. Eighty-six per cent had had at least one prior episode, with 75% having been ill for a period of at least 3 months. Approximately 23% of the sample had definite delusions during the baseline period and were classified as 'psychotic depressions'. The average score and standard error on the Hamilton Rating Scale (1960) for the sample when treatment began was 28·4 ± 0·80 ($N = 130$). Other details on the demographic and clinical characteristics of the study samples are presented elsewhere (Secunda *et al.* 1980; Croughan *et al.* 1986).

Research design

To determine when the drugs begin to act, and to identify early effects which are specifically associated with later recovery, it is necessary to contrast effects in patients who clearly respond to drug treatment with those effects in patients who show minimal or no clinical response to the same drug treatment. To accomplish this objective:

(1) only those patients who showed a clear categorical response, i.e. recovered or showed no change with treatment, were compared[1]†. Patients whose response following 4 weeks was in the minimal to moderate range had to be considered 'indeterminate', since their final response and eventual outcome could not be assessed within the 6 weeks experimental protocol;

(2) patients who showed a significant, positive response to placebo and/or hospitalization during the first two weeks of admission were removed from the treatment phase of the study;

(3) the specifics of change in the affect, behavioural and cognitive functioning of study patients were analysed early, i.e. within the first week of the treatment process.

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† The notes will be found on p. 308.

Baseline period

All patients were maintainec
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Treatment

After the 15-day 'washout' per
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these, nine (14%) did not comp
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Baseline period

All patients were maintained on placebo during an initial two week 'washout' period prior to the beginning of the 4-week drug treatment period. Clinical response during the placebo period was measured through the Hamilton and global severity rating scales. Regardless of initial level, a patient was not included in the treatment study if by day 14 he or she was no longer judged to be suffering from a primary major depressive disorder. Using the diagnostic criteria described, five subjects or 3·8% of the patient sample were separated from the study for this reason.

To examine the clinical course maintained by all patients during the 2-week placebo period, measures of overall severity of the depressed state, as well as of specific state components (Katz *et al.* 1984), were plotted across the three points, the baseline (3rd day following admission), the end of the first week of placebo treatment, and prior to the initiation of drug treatment (approximately the 12th day of placebo). Graphs for each of the three responder groups on a continuous outcome measure of *severity of depressed state* (which includes the Hamilton total score) are presented in Fig. 1. Assessing the size of the component differences on each of the 3 days using analysis of variance, indicated none of any significance.

The patterns of effects across the three days for the three response groups were the same on all of the components (no significant interactions of response type and effect). These patterns indicated relative stability of the depressive condition and its major aspects during this period, and reflected the resistance of these severe disorders to placebo treatments.

Treatment

After the 15-day 'washout' period patients were randomly assigned to imipramine and amitriptyline. The maximum dosage of 250 mg daily was reached for 87% of the patients within 1 week.[2] For 13% of the patients side effects made it necessary to reduce the dosage to 100 to 200 mg daily for the treatment period.

Of the initial 125 patients who entered the treatment phase of the experiment, 64 were assigned to amitriptyline, 61 to imipramine. Of these, nine (14%) did not complete the amitriptyline protocol, and 12 (19%) did not complete the imipramine protocol. None of these patients remained in the protocol sufficiently long to be classified as to type of response. Maas *et al.* (1980) have provided details on the pretreatment and drug treatment protocols and on reasons for dropouts.

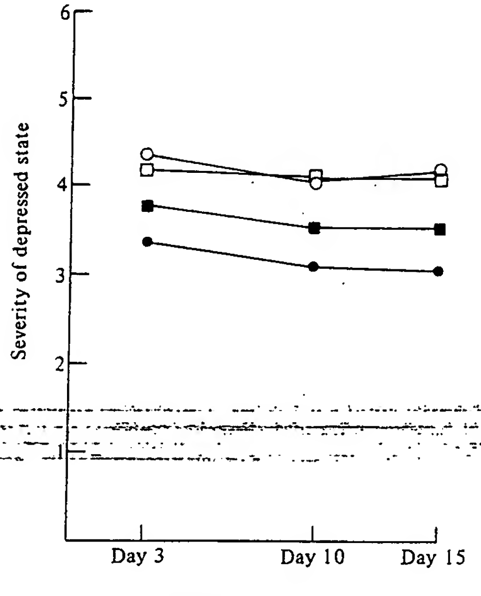

Fig. 1. Depressed state: mean values for 3 pre-treatment days for each outcome group. ●——●, Recovered; □——□, indeterminate; ○——○, non-recovered; ■——■, all cases.

The data presented in this paper were therefore obtained from the sample of 104 depressed patients who completed a baseline period of study, as well as a 4-week period of drug treatment with either amitriptyline or imipramine.

Measurement of the components of the depressed state

Based on a review of research on the major components of behaviour, affect and expressivity in the clinical state (Katz *et al.* 1984), an extensive inventory of methods was selected for the 'multivantaged'[3] analysis of depression. Table 1 describes the several vantages and the methods that were used for each.

Following administration of the set at baseline, analysis of the various methods and their scales led to a set of 11 *state constructs* which measure the major components of depression. Each construct comprises one or more sub-

Table 1. *Methods for measuring state constructs*

I. *Observational ratings*
  A. 'Live interview' (clinician)
    1. Hamilton depression rating scale†
    2. SADS-change scale
    3. Video interview scale
  B. Video interview (clinicians at different centres)
    1. Video interview behaviour and symptoms scale (VIBES)
    2. Ching K-S social behaviour
    3. Expressive movement scale
    4. Hamilton depression scale
  C. Ward behaviour (nurse)
    1. Affective disorder rating scale (ADRS)
    2. Mood scale (Raskin)
    3. Global ward behaviour scale (GWBS)

II. *Patient testing*
  A. Self-report scales
    1. Symptom checklist 90 (SCL 90)
    2. Mood scales
  B. Psychomotor performance
    1. Reaction time
    2. Tapping speed
    3. Visual tracking

† See text for literature references to the scales.

factors which represent the different vantages. A summary of the developmental approach, the factor composition of each construct and their psychometric qualities, has been published (Katz *et al.* 1982).

Measurement of the specifics of drug action was initiated following the first week of treatment and conducted at approximately weekly intervals throughout the treatment period.

Measuring categorical recovery

The evaluation of treatment outcome was fixed in the protocol at four weeks after treatment. At that time, it was evident that a large majority of the patients had either a clearly 'good' or 'poor' response to treatment, making a categorical measure of response more appropriate than a continuous one.

The procedure for classifying patients as responders (essentially recovered) or non-responders (essentially unrecovered or showing only minimal improvement), was based on the measurement of two major dimensions of overall outcome, *general psychopathology* and *severity of the depressed state*.

Essentially, patients in the recovered group had to return to an illness level of no greater than 'mild' severity, demonstrate markedly reduced severity scores, and be reported as having a level of functioning on the Global Assessment Scale (GAS) (Endicott *et al.* 1976) which would indicate no further evidence of psychiatric disorder (> 60). Non-recovered patients show minimal to no decrease on the severity of illness scale, i.e. are still judged to be moderately ill or worse, show a zero to minimal increase on the global improvement scale, continue to have a Hamilton score above 16, and show a level of functioning on the GAS which reflects the continued 'presence of severe symptomatology or impairment'. Further details of the operational criteria for classification are in Katz *et al.* (1984).

Using this system, it was found that recovery occurred in about 50% of the sample over the course of four weeks, with 20–25% of the sample showing a minimal to no treatment response, a rate of response which would be expected from results of earlier controlled trials of the tricyclics with similar patient groups.

RESULTS

Assessing the clinical efficacy of the drugs over the four-week treatment period

In terms of the categorical system and the constructs for determining treatment outcome at 4 weeks: (1) two-thirds of patients achieved marked improvement (with 51% recovery); (2) the two drugs did not differ in the proportion of recoveries effected or in the extent of overall improvement produced; (3) the unipolar and bipolar subtypes did not differ in the proportions of responders and non-responders to amitriptyline or to imipramine; (4) when responders only were compared, there were no significant differences between the actions of amitriptyline and imipramine in reducing overall severity or on any of the 11 major components (constructs) of the depressed state, with one marginal exception – imipramine was apparently more effective than amitriptyline in reducing cognitive impairment in bipolar patients ($P < 0.05$), (see Croughan *et al.* 1987, for further details on efficacy).

The timing and the recovery-related actions of the drugs during the treatment

The large majority of patients had a categorical response of recovery (51%) or non-response (26%) by the end of the 4-week treatment period.

Table 2. *State and outcome*

State constructs
Depressed mood
Anxiety
Retardation
Agitation
Hostility
Somatization
Distressed expressi
Interpersonal sensi
Positive adaptation
Cognitive impairm
Sleep disorder
Outcome constructs
Depressed state
General psycho-pat

† The sample sizes available for each co
‡ Subjects in the three groups were com
follows: § recovered indeterminate and no

Prior to comparing chan
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the 4-week treatment period.

Table 2. *State and outcome constructs: baseline values by outcome group (mean ± standard error (sample size))*

	Recovered group†	Indeterminate group	Non-recovered group	*P* value‡
State constructs				
Depressed mood	4·46 ± 0·21 (54)	5·80 ± 0·29 (24)	5·29 ± 0·30 (26)	0·0011§
Anxiety	3·62 ± 0·22 (45)	4·61 ± 0·32 (20)	4·11 ± 0·24 (22)	—
Retardation	3·23 ± 0·17 (47)	3·48 ± 0·21 (19)	3·46 ± 0·23 (23)	—
Agitation	1·78 ± 0·11 (47)	2·50 ± 0·20 (21)	2·08 ± 0·14 (24)	0·0032‖
Hostility	1·10 ± 0·13 (47)	1·51 ± 0·21 (21)	1·24 ± 0·19 (23)	—
Somatization	2·73 ± 0·14 (54)	3·34 ± 0·25 (24)	3·04 ± 0·20 (27)	—
Distressed expression	2·40 ± 0·15 (54)	2·93 ± 0·23 (24)	2·72 ± 0·28 (27)	—
Interpersonal sensitivity	2·18 ± 0·19 (49)	2·49 ± 0·32 (21)	2·52 ± 0·37 (24)	—
Positive adaptation	3·53 ± 0·22 (43)	2·68 ± 0·24 (19)	3·30 ± 0·30 (21)	—
Cognitive impairment	2·60 ± 0·12 (50)	3·19 ± 0·22 (22)	3·23 ± 0·19 (24)	0·0085§
Sleep disorder	5·32 ± 0·38 (54)	6·13 ± 0·53 (24)	5·59 ± 0·47 (27)	—
Outcome constructs				
Depressed state	3·01 ± 0·18 (49)	4·08 ± 0·26 (21)	3·93 ± 0·27 (24)	0·0011§
General psycho-pathology	3·00 ± 0·13 (49)	3·45 ± 0·26 (21)	3·50 ± 0·20 (23)	—

† The sample sizes available for each construct measure varied; the sample sizes for each of the measures is in parentheses.

‡ Subjects in the three groups were compared using analysis of variance. Multiple comparisons on significant ANOVAs are indicated as follows: § recovered indeterminate and non-recovered; ‖ recovered/indeterminate.

Prior to comparing changes between the recovered group and the non-responders following 1 week of treatment, their baseline construct values were examined. To provide a background for subsequent analyses, the values for the indeterminate group were also included (Table 2).

The three groups were initially compared at baseline on two summary scales of severity of the disorder, *depressed state* and *general psychopathology*, (Katz *et al.* 1984). Both the indeterminate and non-recovered response groups significantly exceeded the recovered group on the depressed state construct. In the light of this difference in general severity, the three groups were examined on each of the 11 state constructs through application of an analysis of variance. To assess the significance of differences among the three groups, a criteria of 0·01 was used to control for inflation of Type I error. The recovered group, although severely depressed, was found to be less depressed in mood and less cognitively impaired[4] than each of the other two groups. The indeterminate and non-recovered groups showed no difference at baseline on any of the state constructs, or on the severity of disorder indices.

The next question was whether specific changes could be identified in patients who would later recover, changes which were not present in non-responders: (a) after 1 week and (b) after 2½ weeks of treatment (the indeterminate group was not included in the following analyses).

The drug groups were merged for these analyses, since when studying responders only there were virtually no differences in the actions of imipramine and amitriptyline on either overall severity or on the major components of depression.

The recovered and the non-recovered groups following one week of treatment

The mean values for change at one week are shown in Table 3. The recovered group changed moderately on a number of aspects (average decreases of 20% or more), depressed mood, anxiety, somatization, distressed expression, interpersonal sensitivity, cognitive impairment, and sleep disorder. The non-recovered group showed a significant reduction only on sleep disorder, with modest increases on anxiety and hostility.

To test whether the two groups were different at 1 week, when changes on all variables were considered simultaneously, a multivariate Hotelling's T^2 (Morrison, 1967) was conducted using residual values for the state constructs, i.e. change scores with the relationship between baseline and one week post-treatment scores

Table 3. *Recovered v. not-recovered patient groups: comparison of affective, behavioural and cognitive changes at 1 week and 2½ weeks of drug treatment (mean ± standard error (sample size)†)*

	Recovered			Not-recovered			Difference in change	
	Pre-treatment ($N = 44$–53)†)	1 week ($N = 42$–54)	2½ weeks ($N = 44$–53)	Pre-treatment ($N = 21$–27)	1 week ($N = 21$–27)	2½ weeks ($N = 21$–27)	1 week	2½ weeks
State constructs								
Depressed mood	4·49 ± 0·22	3·50 ± 0·23	2·53 ± 0·23	5·42 ± 0·34	5·20 ± 0·47	5·40 ± 0·32	0·77**	1·94***
Anxiety	3·89 ± 0·23	3·10 ± 0·21	2·67 ± 0·17	4·31 ± 0·26	4·39 ± 0·29	4·60 ± 0·26	0·87***	1·51***
Retardation	3·15 ± 0·15	3·09 ± 0·17	2·39 ± 0·14	3·53 ± 0·24	3·62 ± 0·26	3·62 ± 0·23	0·15	0·85***
Agitation	2·19 ± 0·12	1·87 ± 0·11	1·64 ± 0·09	2·39 ± 0·15	2·40 ± 0·20	2·33 ± 0·16	0·33**	0·49***
Hostility	1·44 ± 0·15	1·18 ± 0·14	0·99 ± 0·14	1·89 ± 0·26	1·98 ± 0·26	2·29 ± 0·25	0·35**	0·95***
Somatization	3·21 ± 0·16	2·55 ± 0·12	1·91 ± 0·10	3·53 ± 0·20	3·19 ± 0·22	2·99 ± 0·19	0·32	0·76***
Distressed expression	2·40 ± 0·20	1·53 ± 0·18	0·89 ± 0·14	2·77 ± 0·32	2·90 ± 0·36	2·71 ± 0·32	1·00***	1·45***
Interpersonal sensitivity	1·74 ± 0·21	1·26 ± 0·21	1·02 ± 0·18	2·09 ± 0·48	1·61 ± 0·31	2·25 ± 0·42	0	0·88***
Positive adaptation	4·40 ± 0·27	4·23 ± 0·26	5·03 ± 0·23	3·97 ± 0·39	3·68 ± 0·39	3·46 ± 0·20	−0·12	−0·12***
Cognitive impairment	2·68 ± 0·14	2·13 ± 0·13	1·67 ± 0·11	3·41 ± 0·27	3·16 ± 0·24	3·25 ± 0·19	0·30**	0·85***
Sleep disorder	5·31 ± 0·39	3·44 ± 0·36	1·84 ± 0·26	5·59 ± 0·47	3·38 ± 0·44	3·17 ± 0·43	−0·34	1·05**
Outcome constructs								
Depressed state	3·31 ± 0·18	2·49 ± 0·18	1·79 ± 0·18	4·05 ± 0·29	3·83 ± 0·34	3·93 ± 0·24	0·44*	1·22***
General psychopathology	3·09 ± 0·12	2·68 ± 0·12	2·26 ± 0·12	3·61 ± 0·20	3·36 ± 0·22	3·58 ± 0·17	0·16	0·80***

† The sample sizes for each construct varied; the range for each construct is shown in parentheses. These values are for cases with both baseline and treatment data.

‡ P values are from analyses of covariance on the treatment value of each measure covarying for the baseline value: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

partialled out (Wittenborn, 1966). The difference between the groups was significant ($T^2 = 32.58$, $F = 2.53$, 11, 57 df, $P < 0.05$).

To determine which of the 11 mean differences contributed to the significant T^2, univariate tests were applied to differences for each of the state constructs, setting alpha at 0·01 to correct for inflated Type I error. Since the two groups differed at baseline on severity of the depressed state and on specific state constructs, analyses of covariance were applied to tests of differences in type and amount of change at 1 and at 2½ weeks.

The results in Table 3 indicate that the amount of change from baseline to 1 week of treatment was significantly greater for the recovered than the non-recovered on 6 of the constructs. It is noted also, that several constructs clearly did not show differences between the groups at week 1. They included psychomotor retardation, somatization and sleep disorder. To understand the sources of these significant differences at 1 week, the actual changes in the two groups recorded in Table 3 and as shown in Figs. 2 to 4, can be compared.

In summary, the pattern of changes indicates that in those patients who will recover with 4 weeks of treatment, the drugs begin to act within the first week. These early actions appear to be primarily on anxiety, the physical expression of distress, cognitive impairment, and depressed mood.[5] They also include, however, the stemming of increases in anxiety and hostility, increases which occurred in patients who did not respond to tricyclic drugs. The drugs appeared to reduce sleep disorder markedly in depressed patients as a group, but these effects were not necessarily associated with clinical response or later recovery. Retardation and social behaviour did not on the average change very much during the first week, regardless of whether patients responded therapeutically to the drugs.

At two-and-one-half weeks of treatment

As can be seen in Table 3, the differences in the amount of change between the two groups at 2½ weeks are quite large on almost all of the constructs. The T^2 analysis, similar to that conducted with the week one data, indicated that the recovered and the non-recovered groups represented two different populations ($T^2 = 81.06$, $F = 6.30$, 11, 58 df, $P < 0.0001$). Whereas improvement was evident on almost all aspects of the condition for the recovered group,

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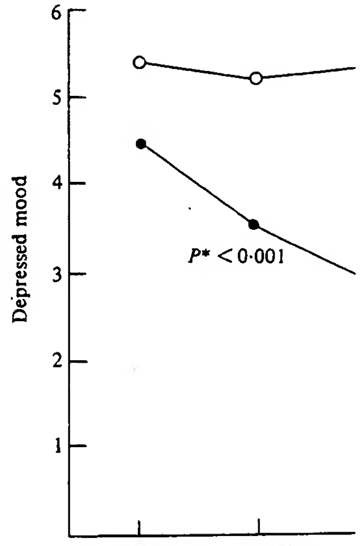

Fig. 2. Depressed mood: mean values during tre
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Application of early change findin
prediction

Having found detectable therape
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f affective, behavioural and
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red		Difference in change	
7)	2½ weeks (N = 21–27)	1 week	2½ weeks
17	5·40 ± 0·32	0·77**	1·94***
19	4·60 ± 0·26	0·87***	1·51***
16	3·62 ± 0·23	0·15	0·85***
10	2·33 ± 0·16	0·33**	0·49***
16	2·29 ± 0·25	0·35**	0·95***
12	2·99 ± 0·19	0·32	0·76***
16	2·71 ± 0·32	1·00***	1·45***
11	2·25 ± 0·42	0	0·88***
19	3·46 ± 0·20	−0·12	−0·12***
14	3·25 ± 0·19	0·30**	0·85***
14	3·17 ± 0·43	−0·34	1·05**
14	3·93 ± 0·24	0·44*	1·22***
12	3·58 ± 0·17	0·16	0·80***

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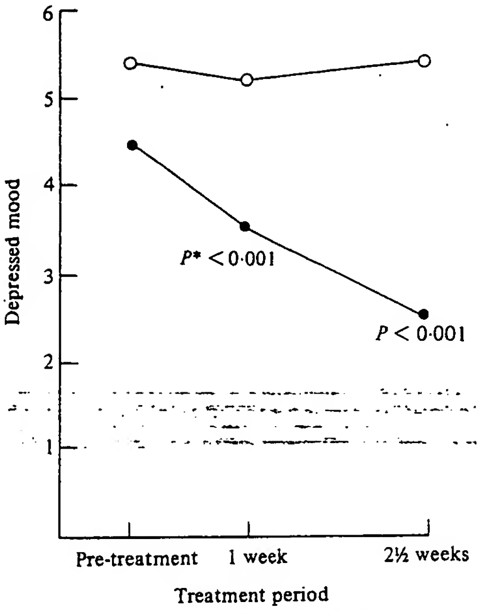

Fig. 2. Depressed mood: mean values during treatment for recovered and non-recovered. ●——●, Recovered; ○——○, non-recovered. *Mean change from baseline different for two groups.

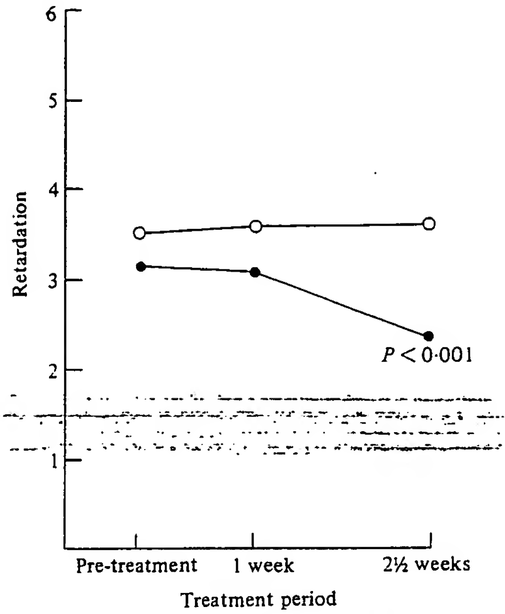

Fig. 3. Retardation of movement and speech: mean values during treatment for recovered and non-recovered subjects. ●——●, Recovered; ○——○, non-recovered.

it was only on somatization and sleep disorder that improvement continued to occur in the non-recovered group. Based on an analysis of covariance for each of the constructs, the difference in amount of change between baseline and 2½ weeks of treatment for the recovered is significantly greater than that for the non-recovered at beyond the 0·01 level of confidence, on all the constructs. Even at this advanced point in the treatment course, the difference between the two groups on sleep disorder was relatively small, both groups showing significant improvement in this area (Fig. 4).

As can be seen in Figs. 2 and 3, where changes in the constructs are graphed over time, the differences between the two response groups at the 2½ week point are increased and large. Furthermore, the results in Table 3 demonstrate a 'cascading' effect, where various changes in the responders appear to merge with the process of recovery itself.

Application of early change findings to clinical prediction

Having found detectable therapeutic actions in the recovered group by the end of the first week, the next practical question was whether such changes were sufficiently large to be 'visible' to clinical observers or detectable through patient self-reports alone.

The objective was to determine whether patients who would recover during the four week course of treatment could be identified by the end of the first week of treatment. Since the issue was one of distinguishing responders from *all* admitted patients, it was now necessary to use the entire sample. The indeterminate and non-responder groups did not differ in profile or level of psychopathology at baseline and thus could be merged for these analyses (Table 2). Emphasis was on the analysis of the one week results, since the group differences were relatively large and clearly discriminating at that point.

Assessing the size of the effects of the drugs following one week of treatment

When the indeterminate was merged with the non-recovered group, the earlier clear distinction between the responder and non-responders on pattern of change at one week was maintained. (Discriminant function analysis, $F = 2·00$, 11, 59 df, $P < 0·05$).

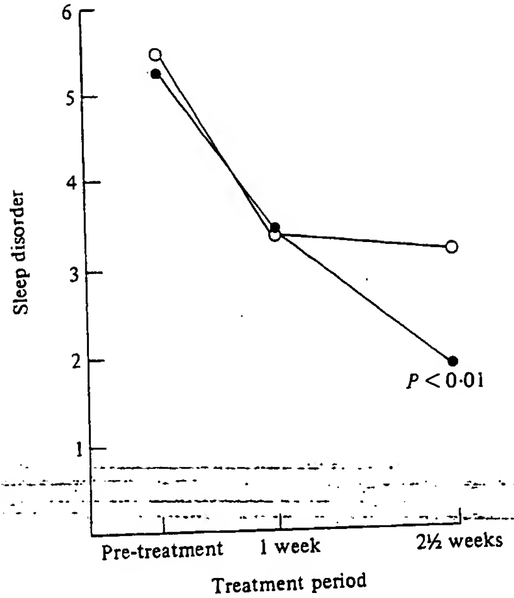

Fig. 4. Sleep disorder: mean values during treatment for recovered and non-recovered subjects. ●——●, Recovered; ○——○, non-recovered.

The changes in the two groups on the constructs and factors are shown in Table 4.

To determine whether differences in change between the two groups were detectable through more than one perspective, i.e. clinicians, nurse and patient self-ratings, the separate factors comprising the state constructs were examined. Discriminant function analyses indicated that from all 3 standpoints, (clinician, nurse and self-ratings), the pattern and the extent of changes in the responder and non-responder groups were different.

For the clinician to be able to identify responders, the differences in amount of change between the two groups, would need to be great enough to be detectable. The changes in each group must, in view of known initial differences, also be assessed relative to baseline values.

The size of the differences in change at week 1 were then examined on each of the method factors, utilizing a statistic which provides a practical estimate of whether the size is large enough to be both detectable and visible. The index used is based on Cohen's *d* (1969). The 'effect size' is the difference between the mean values for the responder and non-responder groups on any given variable, divided by the average of the standard deviations of the two groups, and is expressed in standard deviation units. A score of 0·2 units would be considered small in size; a score of 0·5 standard deviations, medium and 0·8 would be considered as reflecting a relatively large difference. Medium-sized effects are viewed by Cohen to be large enough to be 'visible' to the naked eye. The implication is that the larger the size of the difference between the mean ratings in the two groups, the more likely it is that the difference is 'visible' or detectable in practice. The magnitude of each of the differences in adjusted means is expressed using the effect size measure (Table 4).

The greater reductions in anxiety and depressed mood which occurred in the recovered group, when compared with the non-recovered, were perceived from more-than-one vantage; by clinician, nurse, and patient for the former, and clinician and nurse for the latter construct (Effect size column in Table 4). Patients in the recovered group, for example, did not report significantly greater change on depressed mood. The largest effect sizes for differences in change occurred for the construct measure of anxiety (0·90), and for doctor ratings of depressed mood (0·85). Patient self-ratings of hostility, which changed little in the non-recovered and also showed a significant decrease in the recovered, resulted in a relatively large effect size (0·70). This latter difference in change was not observed by the clinicians or nurses.

The results indicate that clinician ratings after one week of treatment were clearly capable of detecting changes in the general state between the groups, in the specific affects of depressed mood and anxiety, and in the physical expression of this distress. Patient reports of levels of anxiety and hostility decrease significantly when the response to tricyclics is likely to lead to recovery.

The effect size of the above changes is large. The average amount of change for a patient in the responder group after 1 week would be greater in those aspects than that occurring in 75 to 80% of the non-recovered group.

A discriminant function analysis of changes in the two groups conducted at the 2½ week point in treatment resulted, as would be expected, in a very high level of discrimination $P < 0{\cdot}0001$) and consequently in a high level of prediction of

Table 4. *Recovered v. combine affective, behavioural and cognit*

	Pre-treat (*N* = 47·
State constructs and factors	
Depressed mood	4·49±
Self-report	4·34±
Clinician	5·61±
Nurse	3·58±
Anxiety	3·89±
Clinician	4·42±
Nurse	3·53±
Self-report	3·79±
Agitation	2·19±
Clinician	2·64±
Nurse	1·84±
Hostility	1·44±
Self-report	1·96±
Nurse	0·95±
Somatization	3·21±
Distressed expression	2·40±
Interpersonal sensitivity	1·74±
Cognitive impairment	2·68±
Confusion	0·98±
Impaired Concentration	4·47±
Outcome constructs and factors	
Depressed state	3·13±
Clinician	3·35±
Self-report	3·49±
Nurse	2·69±
General psychopathology	3·09±
Clinician & Nurse	2·97±
Self-report	3·25±

† The sample sizes for each construct varied baseline and treatment data.

‡ Recovered and Combined groups: *P* value baseline value: * $P < 0{\cdot}05$; ** $P < 0{\cdot}02$; *** *P*

§ The denominator for the computation of relationship between the adjusted mean differen

response at 4 weeks. Differences change were discernible from mul on most of the constructs. For ex point patients' reports which had change at 1 week, reported marked in depressed mood in accord witl nurses ratings.

DISCUSSION

In this study the central focus was of action of the tricyclic drugs, a associated with the recovery pro depressive states. Based on a num it has been clear for some time nov

Table 4. *Recovered v. combined not-recovered and indeterminate patient groups magnitude of affective, behavioural and cognitive changes at 1 week of drug treatment (mean ± standard error)*

	Recovered		Combined		Differences in adjusted means‡ 1 week	Effect size 1 week
	Pre-treatment (N = 47–54)†	1 week (N = 46–54)	Pre-treatment (N = 45–52)	1 week (N = 38–51)		
State constructs and factors						
Depressed mood	4·49 ± 0·22	3·50 ± 0·23	5·62 ± 0·23	5·22 ± 0·29	0·66*	0·58§
Self-report	4·34 ± 0·32	3·68 ± 0·33	5·91 ± 0·35	5·48 ± 0·38	0·52	0·34
Clinician	5·61 ± 0·21	3·90 ± 0·25	6·68 ± 0·23	5·87 ± 0·30	1·38***	0·85
Nurse	3·58 ± 0·27	3·01 ± 0·27	4·81 ± 0·29	4·78 ± 0·28	0·99**	0·65
Anxiety	3·89 ± 0·23	3·10 ± 0·21	4·59 ± 0·20	4·49 ± 0·22	0·97***	0·90
Clinician	4·42 ± 0·23	3·35 ± 0·23	5·13 ± 0·18	4·86 ± 0·24	1·16***	0·76
Nurse	3·53 ± 0·31	2·70 ± 0·29	4·12 ± 0·31	3·91 ± 0·24	0·95**	0·67
Self-report	3·79 ± 0·29	3·17 ± 0·28	4·67 ± 0·36	4·84 ± 0·35	1·05**	0·69
Agitation	2·19 ± 0·12	1·87 ± 0·11	2·65 ± 0·13	2·48 ± 0·14	0·40*	0·54
Clinician	2·64 ± 0·16	2·23 ± 0·16	3·25 ± 0·19	2·83 ± 0·21	0·27	0·23
Nurse	1·84 ± 0·14	1·43 ± 0·12	2·07 ± 0·14	2·02 ± 0·13	0·48**	0·65
Hostility	1·44 ± 0·22	1·18 ± 0·14	1·88 ± 0·19	1·87 ± 0·18	0·49*	0·51
Self-report	1·96 ± 0·22	1·33 ± 0·17	2·62 ± 0·29	2·45 ± 0·29	0·81***	0·70
Nurse	0·95 ± 0·13	1·06 ± 0·17	1·14 ± 0·17	1·37 ± 0·20	0·22	0·18
Somatization	3·21 ± 0·16	2·55 ± 0·12	3·67 ± 0·18	3·27 ± 0·17	0·48	0·56
Distressed expression	2·40 ± 0·20	1·53 ± 0·18	2·76 ± 0·23	2·82 ± 0·26	1·06***	0·80
Interpersonal sensitivity	1·74 ± 0·21	1·26 ± 0·21	2·09 ± 0·32	1·87 ± 0·25	0·63	0·64
Cognitive impairment	2·68 ± 0·14	2·13 ± 0·13	3·38 ± 0·18	3·05 ± 0·18	0·63**	0·64
Confusion	0·98 ± 0·13	0·73 ± 0·10	1·23 ± 0·17	1·33 ± 0·16	0·48**	0·57
Impaired Concentration	4·47 ± 0·25	3·59 ± 0·23	5·63 ± 0·25	4·90 ± 0·26	0·73*	0·50
Outcome constructs and factors						
Depressed state	3·13 ± 0·18	2·49 ± 0·18	4·10 ± 0·19	3·82 ± 0·22	0·52*	0·58
Clinician	3·35 ± 0·17	2·13 ± 0·17	4·07 ± 0·18	3·74 ± 0·22	1·16***	0·97
Self-report	3·49 ± 0·29	2·92 ± 0·30	4·80 ± 0·31	4·31 ± 0·33	0·32	0·24
Nurse	2·69 ± 0·24	2·53 ± 0·22	3·67 ± 0·26	3·85 ± 0·25	0·69*	0·53
General psychopathology	3·09 ± 0·12	2·68 ± 0·12	3·56 ± 0·16	3·35 ± 0·17	0·35*	0·47
Clinician & Nurse	2·97 ± 0·09	2·49 ± 0·08	3·26 ± 0·12	3·05 ± 0·12	0·40**	0·63
Self-report	3·25 ± 0·23	2·92 ± 0·21	4·04 ± 0·26	3·90 ± 0·27	0·47	0·37

† The sample sizes for each construct varied; the range for each measure is shown in parentheses. These values are for cases with both baseline and treatment data.

‡ Recovered and Combined groups: P values are from analyses of covariance on the treatment value of each measure covarying for the baseline value: * $P < 0.05$; ** $P < 0.02$; *** $P < 0.001$.

§ The denominator for the computation of the 'Effect size' is the root mean square from the analysis of covariance. Therefore, the relationship between the adjusted mean difference and the 'Effect size' is not necessarily monotonic.

response at 4 weeks. Differences in amount of change were discernible from multiple vantages on most of the constructs. For example, at that point patients' reports which had not indicated change at 1 week, reported marked improvement in depressed mood in accord with doctors and nurses ratings.

DISCUSSION

In this study the central focus was on the timing of action of the tricyclic drugs, and the effects associated with the recovery process in severe depressive states. Based on a number of studies, it has been clear for some time now that tricyclic anti-depressants result in marked improvement in approximately two-thirds of patients and that a substantial number of these patients will (when treated with adequate dosage) be fully recovered within a period of four weeks.

On timing and specificity of drug action

Despite clinical lore and limited evidence that clinical effects do not appear for 2–3 weeks (Coryell *et al.* 1982), it is clear from this study that when drug treatment is going to be effective, significant positive changes in behaviour occur within the first week of treatment.

The earliest changes associated with recovery are in the levels of disturbed affect and cognitive

functioning. The drugs also had an early and sustained impact on such somatic symptoms as sleep disorder, appetite loss, and other physiological aspects, but these occurred in both responders and non-responders.

These findings have implications for an understanding of the mechanisms of tricyclic drug action in depression, and for the prediction of clinical response. The timing of the initial pharmacological actions and the rate of the overall recovery process and its cascading quality, suggests that important neurochemical changes in those depressed patients who will recover are occurring during the first week of treatment. This may, in fact, mean that effects are occurring even earlier than 1 week, a finding which indicates that clinical actions on behaviour do not 'lag' far behind the early neurochemical actions of the drug. More recently, investigators influenced by reports that clinical effects are delayed have focused on the later developing pharmacological effects of anti-depressants. A number of such effects have been observed, e.g. on post-synaptic neurotransmitter receptors (Sugrue, 1983). The current results cast doubt on the view that efficacy can be solely attributed to these later effects. The findings that clinical changes begin early, cascade, and are subsequently sustained for an extended period of time, would imply that early pharmacologic effects, e.g. inhibition of uptake of norepinephrine or serotonin, initiate a series of events in the interaction of neurochemistry and behaviour, which are then stabilized in a currently unknown manner by other later developing pharmacological actions. Frazer *et al.* (1985), in a current review, present an analysis of pharmacological findings which attempt to trace this process.

The nature of the early actions also bring into question the validity of the oft-cited hypothesis that the clinical effects of these drugs can be traced to their 'sedative' action on sleep disturbance and on other signs of physical tension, i.e. other somatic aspects. Although there are significant effects on sleep disturbance and somatic symptoms in the first week, they occur equally in both responders and non-responders. The early differentiating changes associated with recovery are primarily those that occur in the affects and in cognitive functioning. This may mean that in those patients in whom there is a therapeutic effect, the drugs interact with the functioning of certain biological systems which are directly associated with the affects of depressed mood and anxiety and with cognitive states.

Implications for clinical prediction

Clinical characterization of the patients in this study showed that partial and non-responders were significantly more depressed generally, and specifically more depressed in mood and cognitively impaired, than the approximately 50% of patients who later recovered with treatment. The major element of cognitive disorder responsible for distinguishing the response groups was impaired thinking and concentration. The latter results support, in a general way, earlier findings that cognitive disorder, specifically delusional thinking, was predictive of poor response (Glassman *et al.* 1975). Severity of depression in itself has been reported to be a factor in response (Abou-Salleh & Coppen, 1983), suggesting that the psychotic depressives who made up about 23% of this hospitalized population were not exclusively responsible for the reduced response in the recovered group. When we removed the subsample of psychotic patients from the analysis to pursue that issue, severity of depression as a general characteristic still differentiated the responders and non-responders. The specific differences on depressed mood and cognitive impairment, however, were no longer present. Although psychoticism would therefore account for a significant part of the variance, 'severity' in itself remained a discriminating factor.

The conclusion to be drawn from these analyses of baseline differences is that in a population of hospitalized depressions the most severely depressed, including the psychotic depressions, do not respond favourably to the tricyclics. The findings provide further support for the hypothesized curvilinear relationship between treatment response and severity of the disorder, referred to by Abou-Salleh & Coppen (1983) and supported by the findings of Quitkin *et al.* (1984) with outpatient depressions. This set of results, which indicates that both the milder and the most severe variants of the depressive disorders are the least responsive to tricyclics, reflects further the heterogeneity of the depressive disorders. They also provide support for the
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CONCLUSIONS

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view that groups at both ends of the continuum represent qualitatively different forms or types of depression, from those of the moderately severe, i.e. types in which there is a different balance of biological and psychosocial factors in their structure or developmental aetiology.

On the other hand, the very severe depressions may simply require even more intensive drug treatment, i.e. higher dosages and/or longer duration of treatment. Controlled studies of higher dosage or treatment periods of longer than 4 weeks, with the severe and psychotic depressions of the types investigated in this study, would contribute to further clarifying the forms depression takes and to resolving the reasons underlying the heterogeneity of their response to tricyclic drugs.

On identifying responders at one week

Although the capacity to predict outcome from findings at the end of the first week is limited, some of the changes which occur were found to be relatively large and should be visible to clinicians. They include changes in depressed mood, anxiety, and in the physical expression of depression. Certain of these effects on the central mood state were *not* reported by patients, e.g. depressed mood, which may explain why discrepancies have occurred in past research, as to when clinical effects first appear. Changes in the responders were, however, sufficiently large by the end of 1 week, for 79% of patients to be correctly classified regarding their likelihood of recovery following 4 weeks of treatment. Prediction from 2½–4 weeks at an even higher level, although not in itself a major accomplishment, is indicative of the speed and the quality of the recovery process. It reflects the cascading quality of the process as it occurred in a large proportion of patients who would recover within the four week treatment period.

Table 5. *Timing and specificity of tricyclic drug effects: summary of findings differences between responders and non-responders* ($P < 0{\cdot}01$)

Non-responders more severe at baseline	Significantly larger change in responders‡	
	At 1 week	At 2½ weeks
Depressed mood Cognitive impairment Overall severity of depressed state	Depressed mood Anxiety Hostility Distressed expression Cognitive impairment Agitation	All components and overall severity

† Analysis of variance.
‡ Analysis of covariance using baseline value as covariate.

Table 6. *Predicting clinical recovery in depressed sample from baseline and changes following 1 and 2½ weeks of drug treatment. Summary of findings. Differences between responders and all others* ($P < 0{\cdot}01$)

Non-responders more severe at baseline	Significantly larger change in responders	
	At 1 week	At 2½weeks
Depressed mood† Agitation¶ Cognitive impairment‡ Overall severity of depressed state†	Depressed mood‡ Anxiety† Agitation§ Hostility‖ Somatization¶ Distressed expression‡ Interpersonal sensitivity¶ Cognitive impairment‡ Overall severity of depressed state†† General psychopathology‖	All components and overall severity†

Difference in size of change 'visible' to:
† Clinicians, nurses and patients.
‡ Two of three observers.
‖ Patients only.
§ Nurses only.
¶ Difference detectable only by combining two or three vantages.
†† Clinicians only.

CONCLUSIONS

The findings which appear to have direct relevance for understanding the action of tricyclic drugs and for clinical application are outlined in Tables 5 and 6, and described below.

(1) With appropriate tricyclic drug treatment the process of change in those patients who will recover begins within the first week of treatment.

(2) The early changes associated with later recovery are specific; primarily in reductions in the disturbed affects and cognitive impairment (Table 5).

(3) The early improvement of somatic symptoms, specifically sleep disturbance, occurs as expected, but this improvement is not directly

associated with or predictive of recovery (Table 3, week 1).

(4) Changes in those who will recover are substantial at 2½ weeks, involve almost all areas of psychological functioning, and project a 'cascading' quality (Table 5).

(5) Although more easily detected when the various vantage measures are combined, the changes in affect and cognition are sufficiently great at 1 week to be visible to clinicians or to patients alone (Table 6).

(6) Clinicians detect changes in depressed mood and overall severity earlier than reported by patients (Tables 4 and 6). This may account for the discrepancies reported in earlier studies concerning the rate of tricyclic drug action.

Theoretically, and from the standpoint of understanding the basic actions of the drugs, these results suggest that key neurochemical and behavioural changes in depressed patients may be occurring during the first week of drug treatment, open to question the 'clinical lag' hypothesis and need to be considered when designing psychobiological experiments.

The above study was completed with the cooperation and participation of the Collaborative Program Investigators: S. H. Koslow (Project Director), S. Secunda (Deputy Project Director), I. Hanin (Consultant), B. Harris (Protocol Monitor) (National Institute of Mental Health); M. M. Katz (Senior Investigator) (Albert Einstein College of Medicine-Montefiore Medical Centre); J. W. Maas (Chairman) (The University of Texas Health Sciences Center at San Antonio); D. E. Redmond, Jr., A. Swann (Yale University School of Medicine); J. M. Davis, R. Casper, S. Chang, D. Garver, J. Javaid (Illinois State Psychiatric Institute); J. Mendels, D. Brunswick, A. Frazer, A. Ramsey, S. Stern (Philadelphia VA Medical Center); P. E. Stokes, J. Kocsis (Cornell University Medical Center); E. Robins (Washington University School of Medicine, St Louis); J. Croughan (Washington University School of Medicine & Jewish Hospital, St Louis); C. Bowden, R. Shulman (The University of Texas Health Sciences Center at San Antonio). The research was supported by National Institute of Mental Health Grants U01 MH26976, U01 MH26975, U01 MH26977, U01 MH26979, U01 MH26978, U01 MH31921 and U01 MH407775.

NOTES

1 Although no definitive evidence from hospital studies exists, clinical experience indicates that it is highly unlikely that severely depressed patients who show minimal response following 4 weeks of intensive treatment with tricyclic drugs will go on to recovery with prolonged treatment.

2 Although this level of dosage is viewed in the United States as optimal for the treatment of hospitalized depressive disorders, it would still be considered high by European standards.

3 'Multivantaged' refers to the fact that the nature of the phenomena of depression are measured through the use of multiple observers, e.g. the clinician and the nurse, in different situations (in this case through observation of behaviour on the ward and in a video recorded interview), and through objective assessment of performance. The adoption of this approach is based partly on the limited state of development of psychological methodology generally for measuring disturbed behaviour, and partly on the differential strengths of various methods. The rationale is further detailed in Katz *et al.* (1982).

4 The measures of the construct, cognitive impairment, were based on the doctor's interview (VIBES) and nurse's ratings (ADRS and GWBS) of the extent of impaired concentration, confusion, of guarded or grandiose thinking, and the patient's self-report of extent of 'cognitive loss' (Katz *et al.* 1984).

5 Since this was not a study of the efficacy of the tricyclic drugs, a placebo treatment group was not included. The absence of a placebo control during the treatment phase prevents concluding that the reported actions were due solely to the medication. Evidence and experience with placebo response of hospitalized and outpatient depressives indicates, however, that the major part of such response occurs within the first week and declines sharply thereafter (Medical Research Council, 1986; Quitkin *et al.* 1984). During the two weeks of placebo treatment, it was shown that no one of the three responder groups in this severely ill sample changed positively on any significant clinical parameter. Further, unlike the experience in outpatient studies, less than 4% of the sample responded to placebo during the first 2 weeks of the study. To further minimize the role of placebo reactivity on drug response, these patients were removed from the treatment phase. Therefore, it is reasonable to assume that only minimal variance can be attributed to placebo or non-specific factors in the analysis of the 1 and 2½ week effects.

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